# Postgraduate Medicine

*Volume 26 · Number 4*

OCTOBER · 1959

OFFICIAL JOURNAL OF THE INTERSTATE POSTGRADUATE MEDICAL ASSOCIATION


## TABLE *of* CONTENTS


Strokes as a Neurosurgeon Sees Them
E. HARRY BOTTERELL, M.D. ..... 413

The Practical Aspects of Anemia Therapy in Pregnancy
ROY G. HOLLY, M.D. ..... 418

Neonatal Jaundice and Prevention of Bilirubin Encephalopathy
WILLIAM J. WATERS, M.D. ..... 425

Juvenile Eczema: Atopic Dermatitis
LOUIS A. BRUNSTING, M.D. ..... 431

Newer Aspects in the Diagnosis and Treatment of Lymphomas and Leukemias
EDWARD SHANBROM, M.D. ..... 436

Diuretics in the Treatment of Hypertension
HARRIET P. DUSTAN, M.D. ..... 446

Urinary Fistulas
CHESTER C. WINTER, M.D., RODERICK D. TURNER, M.D. AND WILLARD E. GOODWIN, M.D. ..... 450

Implications of Maximal Bacterial Resistance to Antibiotics
HARRY SENECA, M.D. AND O. K. TROC, M.D. ..... 457

Special Considerations Regarding Fractures in Children
CHARLES H. HERNDON, M.D. ..... 463

Dysfunctional Uterine Bleeding
WILLIAM C. KEETTEL, M.D. ..... 473

What Is Antral Gastritis?
JOHN M. WEBER, M.D. AND R. DOUGLAS DOSS, M.D. ..... 480

Medical Evaluation of the Patient Before Operation
LLOYD S. RALSTON, M.D. ..... 484


*(Continued on page A-4)*


**Postgraduate Medicine** is published monthly at Minneapolis, Minn., by IPMA Publishing Co., C. Victor Lowrie, executive vice-president; William H. Hull, professional relations manager; Muriel D. Ries, circulation manager; Fred Couzens, Eastern manager, 420 Lexington Ave., New York 17, N.Y., telephone Murray Hill 4-7752; Arthur G. Sullivan, Jr., Central-West manager, 203 North Cedar Street, Horicon, Wis., telephone Hunter 5-2003. Advertising representatives: McDonald-Thompson, 1008 Western Ave., Seattle 1, Wash.; 625 Market St., San Francisco 5, Calif.; 3727 W. 6th St., Los Angeles 5, Calif.; 3217 Montrose Blvd., Houston 6, Tex.; Colorado National Bank Bldg., Denver 2, Colo. Publication date: 10th of the month. Subscription rate $10.00 a year in the United States and Canada; $12.00 in foreign countries. Two volumes a year. Address all editorial and business correspondence to **Postgraduate Medicine**, Essex Building, Minneapolis 3, Minn., telephone Federal 9-8836.

© 1959 by IPMA Publishing Co.

Title Reg. U. S. Pat. Off. Entered as second-class matter February 27, 1947, at the post office at Minneapolis, Minn., under the act of March 3, 1879. Additional entry at Long Prairie, Minn., under date of April 14, 1948. Printed in U.S.A.

Some Problems in Anesthesia for Accident Victims
KARL L. SIEBECKER, M.D. ..... 490

Crisis Types of Abdominal Pain
WALTER C. ALVAREZ, M.D. ..... 495

Clinical Re-evaluation of Daytime Sedatives
ROBERT C. BATTERMAN, M.D., ARTHUR J. GROSSMAN, M.D.,
PAUL LEIFER, M.D. AND GEORGE J. MOURATOFF, M.D. ..... 502

A Training Program in Clinical Pharmacology
LOUIS LASAGNA, M.D. ..... 559

The Countryside of William Withering
HOWARD B. BURCHELL, M.D. ..... A-228

**SYMPOSIUM**

Diagnosis and Treatment of Pancreatitis
ROBERT M. ZOLLINGER, M.D., EDWIN H. ELLISON, M.D.,
DAN W. ELLIOTT, M.D., STANLEY O. HOERR, M.D.
AND WILLIAM D. HOLDEN, M.D. ..... 510

**SCIENTIFIC EXHIBIT**

Streptokinase Buccally in the Treatment of Infection and Edema
JOSEPH M. MILLER, M.D. AND MILTON GINSBERG, M.D. ..... 523

**NUTRITION IN CLINICAL MEDICINE**

A Method for Planning Diets to Lower Serum Cholesterol
PATRICIA A. STEFANIK, M.S. AND MARTHA F. TRULSON, D.SC. ..... 533

**CLINICAL STUDIES**

Treatment of the Premenstrual Tension Syndrome With
Ethisterone and Other Agents
ROBERT S. MUTCH, M.D. ..... 539

Chymotrypsin Therapy of Peptic Ulcer; Results in 78 Cases
A. A. MOZAN, M.D. ..... 542

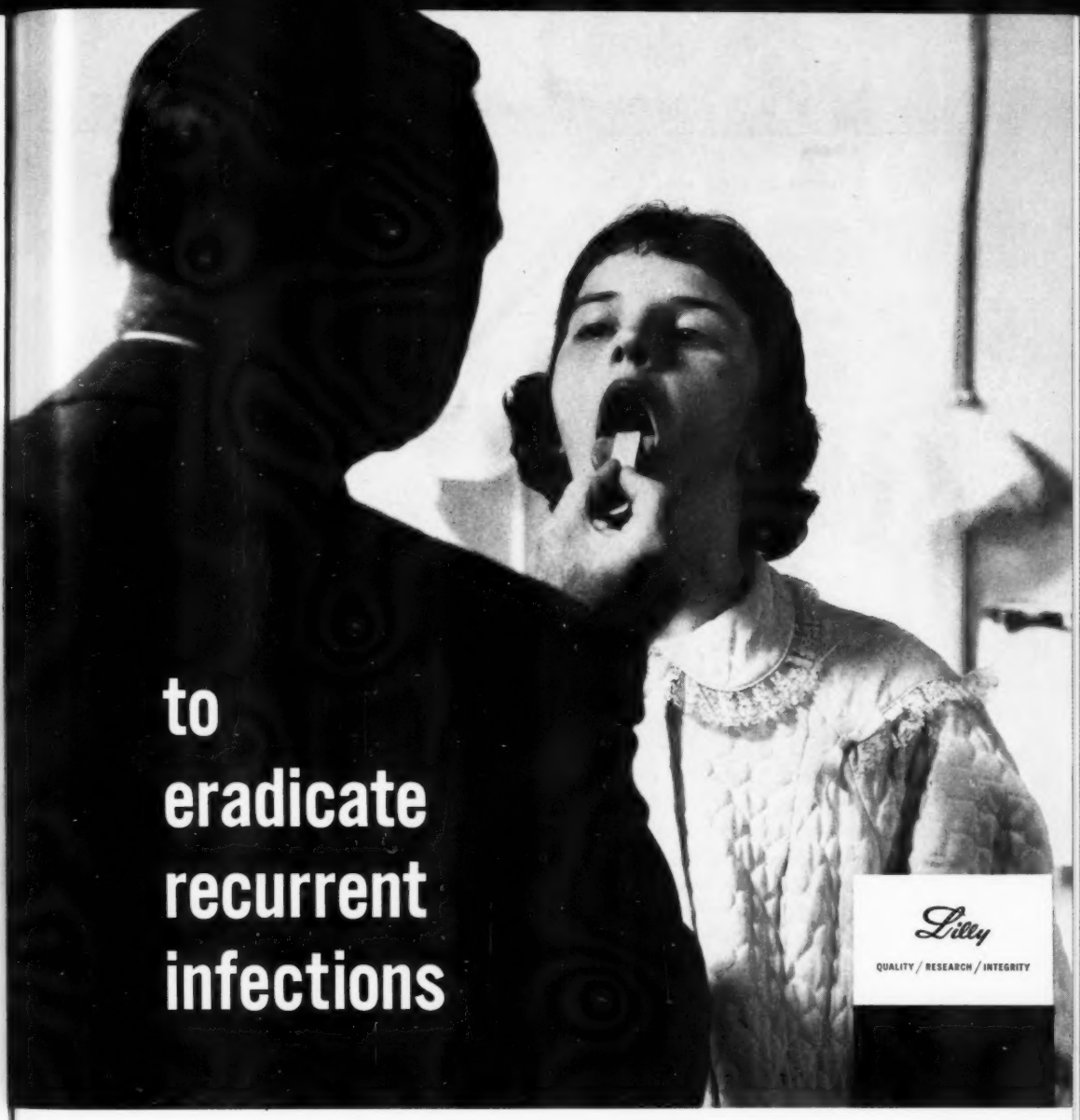
**CLINICOPATHOLOGIC CONFERENCE**

Case Report
FROM THE VETERANS ADMINISTRATION HOSPITAL, HINES, ILLINOIS ..... 551

**SELF-HELP DEVICES**

Garment Fastener
EDWARD W. LOWMAN, M.D. AND HOWARD A. RUSK, M.D. ..... 562

*(Continued on page A-6)*




# LOSONE® WORKS to assure a more decisive response

hen the infection keeps coming back, it may well be that a more decisive antibiotic attack is indicated. such cases, Ilosone consistently provides a prompt, high level of antibacterial activity in the patient's rum. Ilosone is bactericidal against both streptococci and pneumococci and has been reported par- ularly effective against staphylococcus infections in clinical investigation.[1]

ual dosage: For adults and children over fifty pounds, 250 mg. every six hours. For optimal effect, minister on an empty stomach. Ilosone is supplied in Pulvules® of 125 mg. and 250 mg., in bottles 24 and 100.

Ilosone® (propionyl erythromycin ester, Lilly)

1. A.M.A., *170*:184 (May 9), 1959.

LI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

932629

**DEPARTMENTS**

EDITORIALS ..... 564

*Genetics in Medical Research*
*Specialism in Medicine*
*BCG—Pro and Con*
*The Brain of the Elephant*
*A New Population Tendency*

MEETINGS AND POSTGRADUATE COURSES ..... 449, 462

YOUR QUESTIONS ANSWERED ..... A-18

*Intercostal Pain*
*Leukorrhea*
*Herpes Simplex*
*Radioiodine in Diagnosis*
*Hydatid Mole*
*Phalangeal Cyst*

WHAT'S HAPPENING IN MEDICINE ..... Facing A-32-33

LABORATORY NOTES. Ellis S. Benson, M.D. ..... A-42

FORENSIC MEDICINE ..... A-52

The Investigation and Interpretation of Head Injuries
FRANCIS E. CAMPS, M.D.

RADIOLOGY FOR PRACTICING PHYSICIANS. Paul C. Hodges, M.D. ..... A-91

THROUGH THE STETHOSCOPE ..... A-111

MEDICINE FROM ABROAD ..... A-118

NEW FOR YOUR ARMAMENTARIUM ..... A-158

THE MEDICAL BOOKMAN ..... A-190

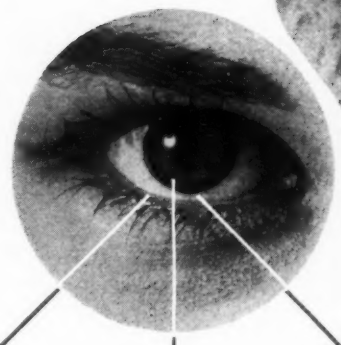
FINANCIAL PLANNING FOR THE MEDICAL PRACTITIONER
J. K. Lasser Institute ..... Facing A-220-221

DR. PEPYS' PAGES. Morris Fishbein, M.D. ..... A-246

THE MEDICAL MUSE. Richard Armour ..... A-252

PRODUCTS BY THERAPY INDICATIONS ..... A-256

INDEX TO TECHNICAL EXHIBITS ..... A-265



common "outer eye" disorders

**allergic**
(allergic blepharitis, allergic conjunctivitis, episcleritis)

**inflammatory**
(acute catarrhal conjunctivitis, ulceration, meibomitis, keratitis)

**traumatic**
(foreign bodies, burns, abrasions, lacerations)

consistently respond to topical therapy with

# METIMYD®

## ophthalmic suspension

**prednisolone 0.5% plus sulfacetamide sodium 10%**

## ointment with neomycin 0.25%

*Tissue destruction is halted, healing is set in motion* by the anti-inflammatory, antiallergic action of prednisolone and the antimicrobial property of sulfacetamide sodium combined in METIMYD Suspension...and for an even wider spectrum of antibacterial effectiveness, neomycin sulfate is added in METIMYD Ointment, the ointment form assuring sustained therapeutic action through the night.

Schering

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

MT-J-239

# *Your Questions answered*

*Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants. Replies are forwarded by mail immediately and selected questions and answers are published each month in this section.*

**• INTERCOSTAL PAIN**

**Q.** A 60 year old man who had a coronary occlusion 10 years ago has had intercostal neuritis for one year. The onset of the condition was gradual, starting with pain and soreness of the precordium. The pain then extended below the left scapula, and this area became extremely tender. Results of all laboratory tests were negative, and x-rays of the spine revealed no pertinent findings. Diathermy, ultrasound, the injection of NOVOCAIN®, and the administration of cortisone and EQUANIL® did not relieve the pain. The patient is now receiving sodium salicylate, and I have considered giving him injections of vitamin $B_{12}$. Can you suggest any further treatment?

M.D.—Florida

**A.** The problems involved in the diagnosis and treatment of pain in the thoracic wall present considerable difficulties. Many of these pains have been termed "intercostal neuritis" or "neuralgia," when the basic difficulty is actually a syndrome of intercostal pain, the exact mechanism of which is uncertain. Such pain ordinarily lacks the flashing characteristics of true neuralgia and frequently does not respond to injections of procaine hydrochloride into the appropriate nerves or nerve roots. If characteristics of nerve root pain are present and if the pain is aggravated by coughing, sneezing or straining at stool and awakens the patient at night, it seems appropriate to carry out spinal puncture. Various therapeutic programs, none of which produces a uniform effect, have been recommended if these characteristics are not present. Cobra venom or injections of foreign protein could be tried, but these measures offer little likelihood of relieving the pain. In most instances, the patient should be encouraged to tolerate the pain and to try to ignore it through the use of sedation, aspirin or tranquilizers when needed.

In summary, the syndrome frequently called "intercostal neuritis" or "neuralgia" is a painful disorder, often of uncertain origin, which responds poorly to any therapeutic measure.

**• LEUKORRHEA**

**Q.** A 32 year old Para III who is six months pregnant has leukorrhea caused by *Trichomonas vaginalis*. After using FLORAQUIN® suppositories for one week, the patient reported that the leukorrheal discharge had stopped but that a dark brown discharge and vaginal bleeding had appeared. Insertion of a vaginal speculum in order to obtain smears also resulted in bleeding. I would appreciate suggestions for treatment.

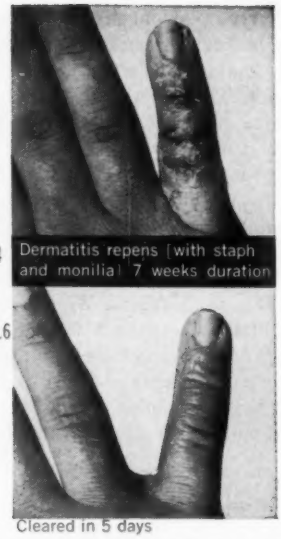
M.D.—Michigan

**A.** This patient's discharge following use of Floraquin suppositories probably was due to an individual sensitivity to the product. There is scarcely a product for the treatment of vaginitis to which some persons are not unduly sensitive.

I would suggest use of low-pressure douching with 3 oz. white vinegar in 2 qt. lukewarm water. The nozzle of the douche should not be inserted more than halfway, and the bag should not be raised more than 18 in. Very few patients react in an untoward manner to this treatment, and it usually keeps them quite comfortable.

*(Continued on page A-20)*

# new for total management of itching,[1,2] inflamed,[3,4] infected[5,6] skin lesions



Dermatitis repens [with staph and monilia] 7 weeks duration

Cleared in 5 days

# Mycolog ointment

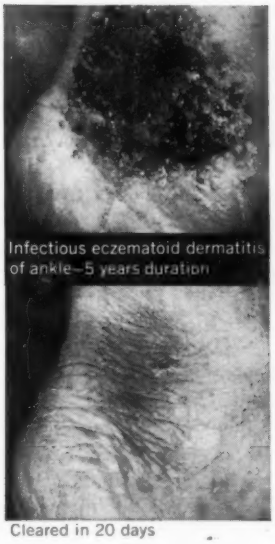
Kenalog, Spectrocin and Mycostatin in Plastibase

## antipruritic/anti-inflammatory/antibacterial/antifungal

**Mycolog Ointment – containing the new superior topical corticoid Kenalog – reduces inflammation,[3,4] relieves itching,[1,2] and combats or prevents bacterial, monilial and mixed infections.[5-7] It is extremely well tolerated, and assures a rapid, decisive clinical response for most infected dermatoses.**

> **"Thirty-one of 38 patients . . . obtained excellent or good control of dermatological lesions . . . [Mycolog] was highly effective, particularly in the management of mixed infections. Several recalcitrant eruptions which had not responded to previous therapy were remarkably responsive to the daily application of this preparation over periods of 2 to 3 weeks."[8]**

**For total management of itching, inflamed, infected skin lesions, Mycolog contains triamcinolone acetonide, an outstanding new topical corticoid for prompt, effective relief of itching, burning and inflammation[1-4] – neomycin and gramicidin for powerful antibacterial action[7] – and nystatin for treating or preventing Candida (Monilia) albicans infections.[5,9]**



Infectious eczematoid dermatitis of ankle—5 years duration

Cleared in 20 days

Application: Apply 2 to 3 times daily. Supply: 5 Gm. and 15 Gm. tubes. Each gram supplies 1.0 mg. (0.1%) triamcinolone acetonide, 2.5 mg. neomycin base, 0.25 mg. gramicidin, and 100,000 units nystatin in PLASTIBASE.


References: 1. Shelmire, J.B., Jr.: Monographs on Therapy 3:164 (Nov.) 1958. • 2. Nix, T.E., Jr., and Derbes, V.J.: Monographs on Therapy 3:125 (Nov.) 1958. • 3. Robinson, R.C.V.: Bull. School of Med., U. Maryland 43:54 (July) 1958. • 4. Sternberg, T.H., Newcomer, V.D., and Reisner, R.M.: Monographs on Therapy 3:115 (Nov.) 1958. • 5. Clark, R.F., and Hallett, J.J.: Monographs on Therapy, 3:153 (Nov.) 1958. • 6. Smith, J.G., Jr., Zawisza, R.J., and Blank, H.: Monographs on Therapy, 3:111 (Nov.) 1958. • 7. Monographs on Therapy, 3:137 (Nov.) 1958. • 8. Howell, C.M., Jr.: North Carolina M.J. 19:449 (Oct.) 1958. • 9. Bereston, E.S.: South. M.J. 50:547 (April) 1957.


And whatever the topical corticoid need, a suitable Squibb formulation is available—Kenalog-S Lotion—7½ cc. plastic squeeze bottles. Each cc. supplies 1.0 mg. (0.1%) triamcinolone acetonide, 2.5 mg. neomycin base and 0.25 mg. gramicidin. Kenalog Cream, 0.1%—5 Gm. and 15 Gm. tubes. Kenalog Lotion, 0.1%—15 cc. plastic squeeze bottles. Kenalog Ointment, 0.1%—5 Gm. and 15 Gm. tubes.

RELIABILITY

**SQUIBB**

**Squibb Quality — the Priceless Ingredient**


"SPECTROCIN"®, "MYCOSTATIN"®, "PLASTIBASE"®, "MYCOLOG" AND "KENALOG" ARE SQUIBB TRADEMARKS

### • HERPES SIMPLEX

**Q.** A 44 year old drug salesman has had recurring herpes simplex since childhood. He has consulted numerous dermatologists without receiving benefit. The eruptions occur about every three months in the form of two or three separate patches on the chin and cheeks, with mild eruptions on the glans penis. A smallpox vaccination administered 10 years ago and courses of injections of crude liver extract did not give concrete improvement.

The attacks are precipitated by fatigue, emotional strain, febrile disorders and by eating chocolate. The patient is otherwise in excellent health; he does not smoke or drink. His family history contributes nothing except that one sister had herpes simplex in her youth. What treatment would you advise in this case?

M.D.—British Columbia

**A.** Everything known in dermatology seems to have been done for the patient. If the eruptions keep recurring in the cheek area, it might be possible to administer 60 r x-ray therapy, half-value layer 0.6 aluminum, at 60 kv once every two weeks for about six doses. This treatment sometimes seems to change the divisions of the virus cells, and has helped in some instances.

### • RADIOIODINE IN DIAGNOSIS

**Q.** What is considered a safe yearly dosage of radioiodine for diagnostic purposes? For example, if 15 mc radioiodine were administered for a 24 hour thyroid uptake test, what would be the permissible number of uptake studies for the patient during a one year period?

M.D.—Ohio

**A.** I do not believe that there is a safe yearly dosage of radioiodine. There does not appear to be any "threshold" in radiation; certainly, no more radiation should be given than is necessary to accomplish its purpose. Changes in thyroid function have been produced by doses as small as 0.5 mc radioiodine. The number of 15 mc doses that could be safely administered in one year would depend on the uptake of the material by the thyroid and on how long the thyroid retained the radioactive material. I cannot think of any situation in which a large number of tracer doses of radioiodine would be necessary for diagnosis.

### • HYDATID MOLE

**Q.** A 34 year old Para VI was seen in what appeared to be the fourth month of pregnancy. She had had a slightly irregular spotting of blood throughout the supposed pregnancy. In the course of one month's observation, the uterus enlarged to a size compatible with a full-term pregnancy, and the bleeding became more profuse. A test for pregnancy gave positive results in a 1:40 dilution of urine. The patient was admitted to the hospital, where she delivered a hydatid mole spontaneously, with severe hemorrhage. Pathologic examination showed the growth to be benign. Curettage was performed, and transfusions were given.

What follow-up care would you suggest?

M.D.—Wisconsin

**A.** Follow-up care of this patient should begin with weekly quantitative determinations of urinary chorionic gonadotropin. If the titer steadily decreases, monthly determinations should be made for the first six months or until two successive negative results are returned. If pregnancy can be ruled out, hysterectomy should be undertaken if the results of the quantitative determinations increase or become positive after having been negative. Curettage should be repeated if bleeding persists or returns after cessation; hysterectomy should be done if curettage does not control hemorrhage. The possibility of subsequent development of chorio-epithelioma necessitates continuous follow-up tests.

### • PHALANGEAL CYST

**Q.** During the past winter, a 56 year old woman has had a cyst on the dorsum of the middle phalanx. It is 1 cm. in diameter, smooth, and painless. What treatment would you suggest?

M.D.—Michigan

**A.** Cysts of the dorsal aspect of the finger usually communicate with a joint, especially when such a cyst overlies the distal interphalangeal joint. If the cyst is directly in the middle of the middle phalanx and is not enlarging and is asymptomatic, it probably could be ignored. If it begins to increase in size, removal should be suggested. During removal, the surgeon should be prepared to trace out the point of origin of the cyst, which would be in either the joint or the synovial sheath of the extensor tendon.

# What's happening in Medicine

POSTGRADUATE MEDICINE'S REPORT of late news of interest to practicing physicians

## NEW TREATMENT FOR HYALINE MEMBRANE

International Congress of Pediatrics:

- Continuous intravenous infusion of glucose and sodium bicarbonate immediately after birth has reduced mortality among premature infants with pulmonary hyaline membrane syndrome. Of 21 dyspneic infants treated, only one died, whereas the mortality was almost 50 per cent among 56 infants placed on the regimen a full day after birth or not at all. The glucose and bicarbonate corrected acidosis and hyperkalemia.—Dr. Robert H. Usher, Royal Victoria Hospital, Montreal.

## THERAPY FOR CEREBRAL INFARCTION

Clinical Congress, American College of Surgeons:

- Intracranial venous hypertension produced in dogs by ligating the superior vena cava appeared to reduce the necrotic area expected after interruption of circulation via the middle cerebral artery. The technic appears to have clinical application in cases of cerebral infarction.—Dr. Guy Owens, Vanderbilt University School of Medicine, Nashville.
- Studies on animals indicate that relatively large concentrations of chemotherapeutic agents can be perfused regionally to the head of a patient who has an intracranial neoplasm without causing severe toxic side effects. Magnitude of the vascular leak of the drug into the general body circulation must be monitored and controlled.—M. S. Mahaley, Jr., Duke University Medical Center, Durham.
- A method of recovering exfoliated malignant cells from enema returns has been used in examining 300 patients, 10 of whom had proved carcinoma of the colon. Malignant cells were demonstrated in the enema returns of nine of these patients, including those with tumors in the ascending colon.—Dr. Alan B. Cameron, Ohio State University College of Medicine, Columbus.

## CRYING PATTERN CLUE TO MENTAL RETARDATION

First International Conference on Mental Retardation:

- Mental retardation may be suspected in early days of life from an infant's crying pattern. Since a baby whose brain is affected has a higher threshold of pain, there is a longer period between stimulus and onset of crying than in a normal child. The crying pattern is often erratic and spasmodic.—Dr. Samuel Karelitz, Long Island Jewish Hospital, New Hyde Park, N.Y.

## "Dual action" theory on insulin

Conference on Diabetes, New York Academy of Medicine:

- Insulin may exert a dual action in the body, which is believed to aid the production of energy from sugar in peripheral body sites, such as muscle, and to regulate the flow of sugar from the liver into the blood.—Drs. Gerson Jacobs and Sidney Weinhouse, Temple University School of Medicine, Philadelphia.
- The reduced ability of the body to use carbohydrates may be the earliest recognizable symptom of diabetes. Of 295 nondiabetic relatives of diabetic patients who were given the cortisone-glucose tolerance test, 25 per cent had positive reactions. Thirty-five of these subjects were given one or more repeat tests over a period of one to five years. Diabetes has since developed in five of them, and tests indicate that four others are probable diabetics.—Drs. Stefan S. Fajans and Jerome W. Conn, University of Michigan Medical School, Ann Arbor.
- Complicating disorders of the nervous system are an integral part of diabetes itself and do not necessarily result from poor control of the disease over a long period. The disorders may occur when the diabetes itself is well controlled. Frequently, neuropathy and symptoms of glycosuria develop simultaneously. An undetermined toxic factor may be responsible for some of the complications.—Dr. Max Ellenberg, Mount Sinai Hospital, New York.

## Prompt treatment for epilepsy advised

Michigan State Medical Society:

- The most important general principle of drug therapy in epilepsy is to start treatment as soon as the diagnosis has been established. In most cases, the degree of success in controlling seizures is directly related to the duration of the disease. Treatment should begin with one drug. Other drugs should be prescribed only when the maximal tolerated dosage of the initial drug fails to produce a satisfactory clinical response. The therapeutic dosage of anticonvulsants varies with the patient. Medication in the same dosage which controlled the seizures should be taken daily for at least four years after the last seizure.—Dr. Samuel Livingston, The Johns Hopkins University School of Medicine, Baltimore.
- The implications of a mass in the neck vary with the patient's age and with the mass's location, consistency, duration and singularity. Initially, the only safe assumption is that the mass is secondary to disease elsewhere. Removal of a lateral cervical mass (node plucking) for diagnosis is unwise unless it has been preceded by an uninformative aspiration biopsy and, sometimes, by a nasopharyngeal biopsy.—Dr. Jerome A. Hilger, University of Minnesota Medical School, Minneapolis.
- General practitioners and pediatricians should be more interested in the psychologic aspects of children, not only from the standpoint of differential diagnosis when psychosomatic illness mocks organic disability, but also because behavior problems in children are too often neglected.—Dr. James G. Hughes, University of Tennessee College of Medicine, Memphis.

## Hypnoanesthesia and perception

Society for Clinical and Experimental Hypnosis:

- Surgical patients under hypnoanesthesia may perceive offhand remarks about their poor prognosis and receive an adverse psychologic impact.—Dr. David B. Cheek, Mount Zion Hospital, San Francisco.
- Alcoholic, aged and debilitated patients make good hypnotherapeutic subjects, probably because of their recognition of the need. In addition, the rapid technic takes effect before the patients with their wandering minds can mobilize criticism.—Dr. Lester A. Millikin, Park Lane Memorial Hospital, St. Louis.

# In the menopause...
## *transition without tears*

## Milprem promptly relieves emotional distress with lasting control of physical symptoms

# Milprem®

Miltown®+conjugated estrogens (equine)

Supplied in two potencies for dosage flexibility:

MILPREM-400, each coated pink tablet contains 400 mg. Miltown (meprobamate) and 0.4 mg. conjugated estrogens (equine).

MILPREM-200, each coated old-rose tablet contains 200 mg. Miltown and 0.4 mg. conjugated estrogens (equine).

Both potencies in bottles of 60.

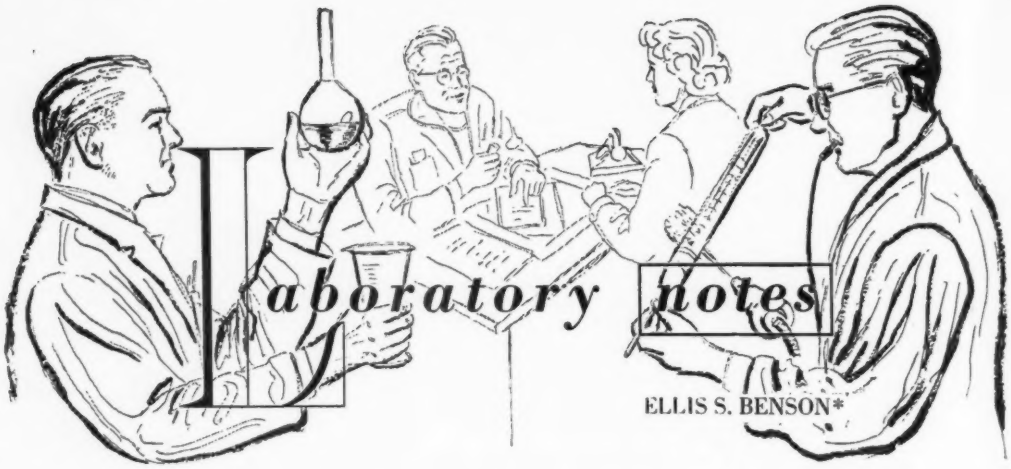
Literature and samples on request.

***In minutes,*** Milprem starts to ease anxiety and depression. It relieves insomnia, relaxes tense muscles; alleviates low back pain and tension headache. As the patient continues on Milprem, the replacement of estrogens checks hot flushes and other physical symptoms.

***Easy dosage schedule:*** One Milprem tablet t.i.d. in 21-day courses with one-week rest periods; during the rest periods, Miltown alone can sustain the patient.

WALLACE LABORATORIES, *New Brunswick, N. J.*

CMP-9224-60




ELLIS S. BENSON*

# Steps Toward Reliable Hemoglobinometry

ALTHOUGH Dr. Sanford[1] discussed the subject of hemoglobinometry in this column a year ago, I know he would not think it amiss for me to consider it again. His lively interest in the subject spanned a quarter of a century. In 1922 he joined Dr. Charles Sheard in developing the first photoelectric colorimeter for the measurement of hemoglobin concentration. This step was a great advance over visual hemoglobinometry. The substitution of a phototube and full instrumentation for the eye in the appreciation of degrees of brightness of light offered new accuracy and dependability. Because this seemed so obvious and because reasonably priced photoelectric instruments became available, methods based on their use supplanted visual methods, influenced as they were by the vagaries of color and brightness. Has this brought us to the promised goal of reliable hemoglobin measurements? The fact that it has not is no reflection on the idea of photoelectric determination, for virtually all commercially available photoelectric instruments are capable of yielding accurate results when properly used.

But instruments are not infallible; they can lie, too. There are instrumental sources of error such as stray light in filter photometers, inconstancy of photo tubes, and fluctuations in the voltage and frequency of the alternating current source. (Manufacturers have belatedly recognized the latter difficulty, and many instruments now are provided with voltage regulators.) Besides these potential sources of error, there is, as Ham[3] states, another disadvantage: "The photoelectric cell always gives an answer and is therefore subject to uncritical misuse." The galvanometer reading may be altered by turbidity of the solution or dirty glassware, artifacts which would be immediately appreciated in visual colorimetry. "The ease of the photoelectric method, thus, introduces a real danger of false confidence in results and lack of control of the instrument."[3] Instrument manufacturers have bolstered this false confidence and done us a disservice by supplying photoelectric colorimeters which are precalibrated for hemoglobin determination and other procedures.

Unfortunately, the calibration of instruments for measuring hemoglobin required considerable technical knowledge and skill, for the methods of calibration were far from simple, depending on the oxygen capacity or iron content of blood. For many small clinical laboratories it was a matter of buying a precali

(Continued on page A-44)

*Director of Hospital Laboratories and Associate Professor of Clinical Laboratory Medicine and of Pathology, University of Minnesota Medical School, Minneapolis, Minnesota.

Gaining the cooperation of your patient is the hardest part in most reducing programs. PET *Instant* Nonfat Dry Milk helps you meet that problem in these ways:

PET *Instant* instead of whole milk for drinking cuts calories in half. Yet it supplies all the essential milk nourishment, except the fat. Used in cooking, it allows the diet to include many foods not permissible when made with whole milk or cream.

Since nonfat milk is the richest source of high-quality protein among the common foods, PET *Instant* helps combat fatigue and create a feeling of satisfaction.

PET *Instant* is a delicious, fresh-tasting beverage—one your patients will enjoy using. It mixes instantly . . . costs only about 8¢ a quart.

Instantized so it dissolves almost at the touch of water.

36.5% Protein (in dry form)
All the calcium and
B-vitamins of whole milk
*without* the fat

©1959

—PET MILK COMPANY • ST. LOUIS 1, MISSOURI—

brated instrument, depending on the kindness of a larger laboratory to assist with the calibration, or having no calibration or standardization at all. Consequently the results of hemoglobin determinations have more often been regarded with suspicion than perhaps any other test. Urgently needed was a simple, dependable means of standardizing hemoglobin determinations. Lack of a stable hemoglobin standard has been a crippling disadvantage. Fortunately, this disadvantage now appears to have been overcome.

In 1953, the Army Medical Service Graduate School took the initiative in this country in establishing a hemoglobin standard.[4] The British previously had had experience with national standardization of methods for measuring hemoglobin. The army conducted an extensive field trial using a cyanmethemoglobin solution proposed by Dr. David Drabkin.[5] The success of this trial was so striking that the National Research Council was asked to explore the possibilities of establishing a national hemoglobin standard for general use throughout the country. A panel was organized which decided early in its deliberations that it would be impractical to establish multiple standards for all the different methods of determining hemoglobin. The widespread use of a single method of analysis would be encouraged. After reviewing several methods, the panel chose Drabkin's cyanmethemoglobin method.[6] One of the reasons for selecting this method was the stability of the cyanmethemoglobin standard, which remained unchanged for up to three years when stored in the refrigerator in sealed ampules. Another reason was its successful use by the army: All six hospital laboratories which used this method checked within 2 per cent in field trials with the standard, while hospitals using other methods showed considerably less agreement.

More than 1000 hospitals throughout the United States cooperated in the trial sponsored by the National Research Council. While some difficulties were encountered, in general, the trial was an outstanding success.[7] As a result of this experience several commercial hemoglobin standards are now available. Cyanmethemoglobin standards are produced by Ortho Pharmaceutical Corporation, Raritan, New Jersey, under the name of ACI GLOBIN® and by Hycell, Inc., 230 Medical Arts Building, Houston, Texas, under the name of Hemoglobin Standard. These standards have been submitted for certification to the College of American Pathologists, which has been designated as the certifying authority for a national standard. These standards come in the form of a solution in sealed glass ampules, and in this form are stable under refrigeration for long periods of time.

It is only fair to state that there are also now available hemoglobin standards other than cyanmethemoglobin. One of these, HEMOTROL®, produced by Clinton Laboratories, Los Angeles, California, is a whole blood hemoglobin standard containing lysed red cells. It appears to be stable for about 14 months when kept in the refrigerator in sealed containers. A whole blood hemoglobin standard is provided by Hema Standards, Inc., P. O. Box 6329, Dallas, Texas. It is said to be stable for three weeks if the supplier's directions are followed. These standards appear to give accurate results, and it is claimed that they can be used to calibrate any method.

These hemoglobin standards provide a link between the absolute reference methods for determining hemoglobin, such as oxygen capacity, iron content and spectrophotometric methods, and the technics generally followed in small laboratories. They should help to make reliable calibrations widely possible and allow frequent checking of calibrations.

A few further comments may be in order concerning the cyanmethemoglobin method. When the national field trial previously referred to was started, only 7 per cent of the cooperating laboratories were determining hemoglobin by the cyanmethemoglobin method, but by the time of the final report on the trial two-thirds of the laboratories were using the method.[7] Why has this method been so widely adopted with enthusiasm? It offers a number of distinct advantages: (1) The procedure is simple and accurate, involving only the addition of a single reagent to a sample of blood.[6] (2) Cyanmethemoglobin is a pig-

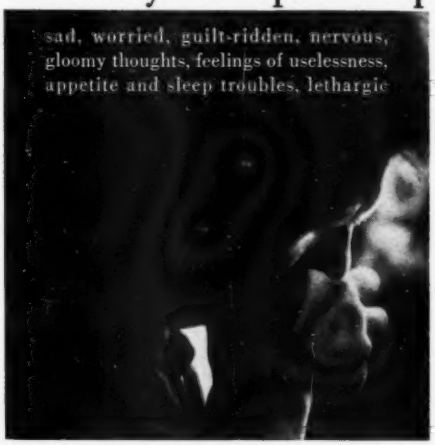
*(Continued on page A-46)*

# now...correct depression safely and rapidly in everyday office practice

# Nardil™

brand of phenelzine dihydrogen sulfate

## restores your depressed patient to purposeful reality




### safely

**No significant reports of toxicity to liver, kidneys or blood[1-3] in thousands of cases to date.**

### rapidly

**Antidepressant activity within the first few days; complete recovery occurs within 2 to 6 weeks.**

### correctively

**Removes the depression itself, does not merely mask the symptoms as do tranquilizers and sedatives.**

Nardil is indicated in the office treatment of all mild to severe depressions; in those related to childbirth, menopause, old age, or those caused by stress situations; when there is a past history of depressed periods, and in depressions associated with chronic diseases such as angina pectoris and rheumatoid arthritis.

*Dosage:* One tablet three times a day.
The above dosage should be maintained until remission of symptoms is achieved which may require 2 to 6 weeks. Dosage should then be reduced to a maintenance level of one or two tablets a day.

*Supplied:* 15 mg. orange-coated tablets, bottles of 100.

*References:* **1.** Sainz, A.: The Phrenopraxic Activity of a Non-noxious Antidepressant, *Ann. New York Acad. Sc.* (in press) 1959. **2.** Thal, N.: Cumulative Index of Antidepressant Medications, *Dis. Nerv. System 20*:197 (May) 1959. **3.** Saunders, J. C.; Roukema, R. W.; Kline, N. S., and Bailey, S. d'A.: Clinical Results with Phenelzine, *Am. J. Psychiat.* (in press) 1959.

WARNER CHILCOTT
MORRIS PLAINS, N.J.

ment which remains entirely unchanged in its spectral-absorption characteristics for 24 hours or more at room temperatures.[8] (3) Its absorption band in the region of 540 mμ is broad and relatively flat; therefore, its color is suitable for measurement in filter photometers as well as in narrow band spectrophotometers (without stray light effects). (4) All forms of hemoglobin in blood can be determined by the method (with the exception of sulfhemoglobin). Thus it approximates total hemoglobin better than other methods. Perhaps because of the dread associated with anything containing cyanide, the poisonous nature of the reagent used in the cyanmethemoglobin method has frequently been overstressed. The lethal dose for man of the dilute solution used approaches 4 l.,[9] and it is less toxic than Hayem's solution, which is used as a diluting fluid in red blood cell counts.[8] The test solution may be obtained under the name of Drabkin's solution from Fisher Scientific Co., 2850 South Jefferson Avenue, St. Louis, Missouri, at a cost of $17 for 12 units, each unit making 4 l. of the test solution.*

Acid hematin photoelectric methods are inaccurate and should be abandoned. They are subject to uncontrollable errors due to the influence on acid hematin of unknown factors in plasma.[10]

The use of stable, accurate standards for calibrating photoelectric methods and rechecking these calibrations from time to time is a major advance in the direction of reliable hemoglobinometry. Of course, it will not compensate for technical inadequacies, dirty glassware or careless pipeting.

Attention has been called to the large errors found in hemoglobin pipets on the market, the error being as high as 30 per cent in some instances.[11, 12] A useful procedure is to obtain for general use Exax Sahli hemoglobin pipets (Kimble)† which have a claimed accuracy of 1 per cent and to check the calibration of these against that of a special pipet which has been certified as to accuracy by the United States Bureau of Standards.‡ This may be done by comparing hemoglobin determinations on a single sample of blood using both the pipet to be checked and the Bureau of Standards pipet. The values should agree within a predetermined range which depends on the degree of accuracy one seeks, say 0.2 gm. If poorer agreement is obtained, the determination should be repeated, and if the values still fail to agree within this range, the pipet should be discarded.

*It is also supplied as Drabkin's reagent by Hartman, Leddon Co., 5821 Market Street, Philadelphia, Pennsylvania, in 8, 16 and 32 oz. bottles and as ACULUTE® in the form of pellets and diluent from Ortho Pharmaceutical Corporation, Raritan, New Jersey. It may be easily prepared in the laboratory from chemical reagents without great danger.[4] Reports on commercial Drabkin's reagents suggest that these are not uniformly of good quality. We and others have used the Fisher product with dependable results. It is important to keep the diluted reagent in a brown bottle to protect it from light.

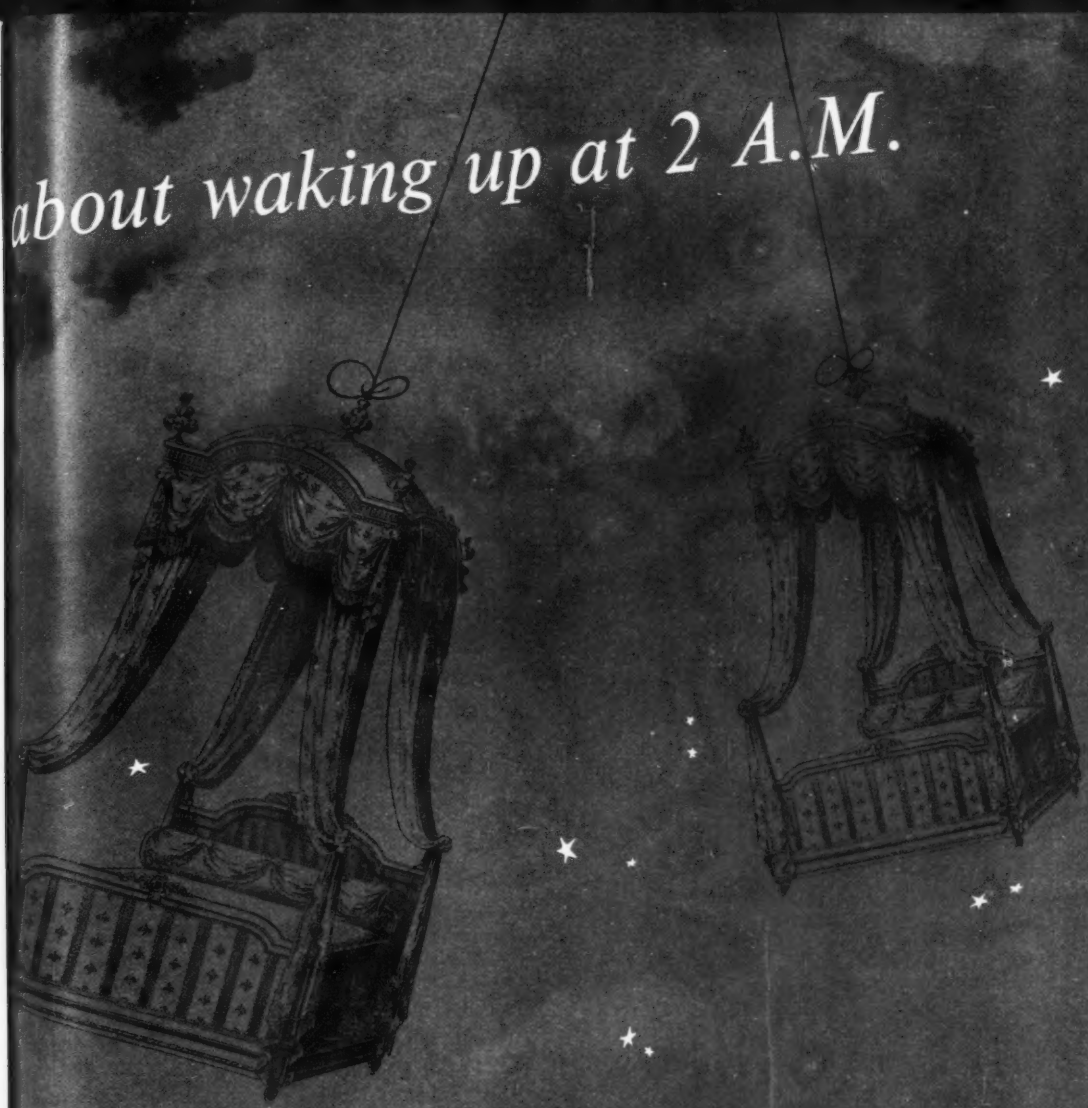
†Owens-Illinois Company, Toledo 1, Ohio.

‡These may be obtained at $4 each from Clay-Adams Inc., 141 East 25th Street, New York 10, New York.

## REFERENCES


1. SANFORD, A. H.: Hemoglobinometry. Postgrad. Med. 24:A-28 (October) 1958.
2. STATES, M. N.: Stray light in filter photometers. Am. J. Clin. Path. 22:403, 1952.
3. HAM, T. H.: Determination of hemoglobin. In A Syllabus of Laboratory Examinations in Clinical Diagnosis. Cambridge, Harvard University Press, 1951, pp. 90-101.
4. CROSBY, W. H., MUNN, J. I. and FURTH, F. W.: Standardizing a method for clinical hemoglobinometry. U. S. Armed Forces M. J. 5:693, 1954.
5. DRABKIN, D. L.: Crystallographic and optical properties of human hemoglobin: A proposal for the standardization of hemoglobin. Am. J. M. Sc. 209: 268, 1945.
6. DRABKIN, D. L. and AUSTIN, J. H.: Spectrophotometric constants for common hemoglobin derivatives of human blood. J. Biol. Chem. 98:719, 1932.
7. CANNAN, R. K.: Proposal for a certified standard for use in hemoglobinometry—second and final report. J. Lab. & Clin. Med. 52:471, 1958.
8. MANN, F. D.: Clinical determination of hemoglobin. Minnesota Med. 35:255, 1953.
9. CANNAN, R. K: Proposal for distribution of a certified standard for use in hemoglobinometry. Clin. Chem. 1:151, 1955.
10. WU, H.: Studies on hemoglobin: The advantage of alkaline solutions for colorimetric determinations of hemoglobin. J. Biochem. 2:173, 1923.
11. ANDERSCH, M. A. and SACKS, M. S.: The hemoglobin pipet as a source of error in photoelectric hemoglobinometry. Am. J. Clin. Path. (Technical Section) 15:105, 1945.
12. LOCKHEAD, H. B. and PURCELL, M. K.: Accuracy of small hemoglobin pipets. Am. J. Clin. Path. 22:296, 1952.

# about waking up at 2 A.M.



# nebralin

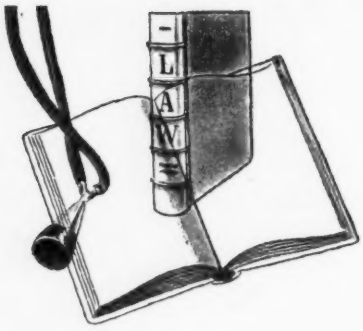
*timed-release tablet*

*timed-release action for a full night's sleep*

NEBRALIN is designed to duplicate the normal sleep pattern. It encourages muscular relaxation and induces sustained, relaxed sleep by the release of Dorsital and mephenesin in a timed-release tablet. Rapid-acting mephenesin quickly relaxes skeletal muscles to overcome "fatigue-tension" and conditions the body for sleep. Dorsital provides CNS sedation to induce sound, relaxed sleep. The initial and sustaining dosages are designed to keep the amount of barbiturate to be inactivated at any one time at a low level tapering toward morning. Evidence indicates that mephenesin is capable of producing sleep,[1] and when combined with a barbiturate enhances barbiturate action.[2, 3, 4] Moreover, the integrated action of the two components permits smaller dosages of each,[2] assuring your patients refreshed awakenings without "morning hangover."

1 Schlesinger, E. B.: Tr. New York Acad. Sc. 2:6, (Nov.) 1948.
2 Richards, R. K., and Taylor, J. D.: Anesthesiology 17:414, 1956.
3 Shideman, F. E.: Postgrad. Med. 24:207, 1958.
4 Berger, F.: Pharmacol. Rev. 1:243, 1949.

SMITH-DORSEY · a division of The Wander Company · Lincoln, Nebraska · Peterborough, Canada




# Forensic Medicine

## The Investigation and Interpretation of Head Injuries

FRANCIS E. CAMPS*

*University of London, London, England*

FRANCIS E. CAMPS

THE investigation of death from head injuries forms a significant proportion of the cases in any practice of forensic pathology. Although it is not always appreciated, the correct interpretation of the findings can be of considerable value in assisting courts to arrive at a proper decision in both civil and criminal cases. Moreover, although eye witnesses may be deceived or deceive, dumb evidence cannot lie and is only subject to human error in interpretation. The latter is usually due to inexperience or to subconscious self-deception. The following case shows the danger of a prejudiced eye witness:

"A man was fatally injured as a result of impact with a police car. Eye witnesses in this part of the city were 'police-allergic' and said the car had run him down. Subsequent reconstruction from injuries to the man and damage to the car revealed the truth—that he had walked into the side of the car."

The value of reconstruction is not restricted to legal medicine, for a knowledge of the mechanism which caused an injury can aid the clinician in diagnosis and treatment and in making a prognosis. It is obvious that a correctly conducted investigation of any head injury, whether the injured person is alive or dead, requires the same approach as does that of any other traumatic lesion.

Although a detailed history of the injured person may be of considerable value, it should be studied *after* the examination; otherwise, the examiner may have a preconceived idea into which he subsequently fits his facts. It usually is unwise to place too much importance on the history unless it is confirmed by evidence based on visual observations of the patient before and after death. This is stated

*(Continued on page A-54)*

*Reader in Forensic Medicine, The London Hospital Medical College, University of London, London, England.

Presented at the eleventh annual meeting of the American Academy of Forensic Sciences, Chicago, Illinois.

PROTECTS AGAINST ANGINAL ATTACKS
RUSSEK: PETN is ". . . the most effective drug currently available for prolonged prophylactic treatment of angina pectoris."[1] Prevents some 80% of anginal attacks.
EASES CARDIAC TENSION
RUSSEK: "I favor ATARAX [as the tranquilizer for the anxious cardiac]...because there is an absence of side effects with this drug, and also because in cardiacs who are troubled with ectopic beats, ATARAX has a quinidine-like action."[2]
PETN + ATARAX®
(pentaerythritol tetranitrate)
(base of hydroxyzine)

# CARTRAX® (PETN + ATARAX)

*Dosage:* Begin with 1 to 2 yellow CARTRAX "10" tablets (10 mg. PETN plus 10 mg. ATARAX)3 to 4 times daily. When indicated, this may be increased by switching to pink CARTRAX "20" tablets (20 mg. PETN plus 10 mg. ATARAX).

For convenience, write "CARTRAX 10" or "CARTRAX 20."

*Supplied:* In bottles of 100.

*References:* 1. Russek, H. I.: Postgrad. Med. *19*:562 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Miami Beach, April 12, 1958.

ROERIG Rx

*New York 17, N. Y.*
*Division, Chas. Pfizer & Co., Inc.*
*Science for the World's Well-Being*

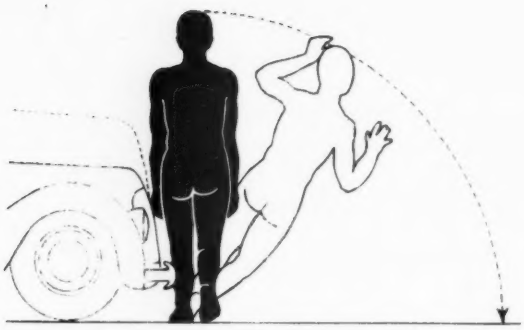


FIGURE 1. Impact from the side.

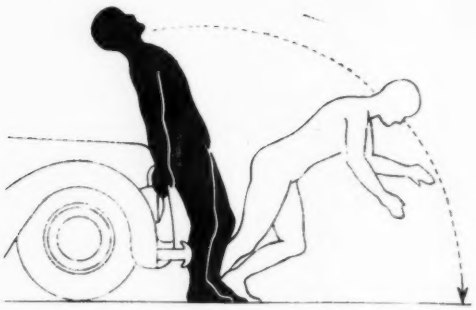


FIGURE 2. Impact from behind.

unequivocally, because there is always the danger that the history may be incorrect and that the examiner may be subconsciously misled. A more practical aspect is that the examiner becomes so accustomed to relying on the history that he may find himself in difficulty when none is available.

### *Technic of Investigation*

The technic of acquiring the necessary data in investigating head injuries may be divided into the following stages. This procedure has proved to be of considerable value, as it affords an opportunity for re-examination at a later date.

*Stage 1*—A general examination is conducted of the clothed body and then of the unclothed body to obtain information regarding such detail as direction of impact. At this stage, many pathologists err, because they fail to examine the clothed body. The presence of material such as glass, flakes of paint, or oil may be of considerable value in reconstructing an accident or in identifying a vehicle. Much valuable evidence on the clothing may be lost through careless handling or destruction. Another error is to allow the body to be washed, as marks and trace evidence may be lost.

The general examination may be of great assistance in assessing traffic accidents, which are the cause of a large proportion of head injuries. Figure 1 shows what may be expected from a sideways impact in a person crossing the road; figure 2 shows the results of an impact from behind.

Injuries can be divided into those of primary impact, caused by the vehicle itself, and those of secondary impact, caused by the person's striking the ground, some other object, or even the vehicle a second time. Since trauma to a fixed head causes a different type of lesion than does injury to a moving head, it is essential to distinguish between injuries caused by primary impact and those caused by secondary impact. Sometimes both injuries may have occurred.

Injuries from primary impact on any body often can be identified from their character and site, which may indicate the points of contact with the vehicle. Certain characteristics may indicate injuries resulting from secondary impact. In the case of assault by blunt or sharp weapons, the presence and site of characteristic defense injuries on the hands or arms may be of assistance in identifying the instrument. Bruising on the face may indicate a blow which has caused loss of balance and consequent impact of the head against the ground. Examination of the eyes, ears, nose and mouth is essential to exclude or indicate any significant disability such as impaired vision or hearing, while a wasted or deformed limb may have caused a fall.

*Stage 2*—All injuries on the face and scalp should be examined, and it should be remembered that they may be caused by striking an object or by being struck. Such lesions may include bruises with or without abrasions. Bruises may show first merely as swellings or tenderness, but there may be some characteristic pattern, such as the weave of the material

*(Continued on page A-56)*

## In skeletal-muscle disabilities . . .

## Curbs spasm, relieves rigidity, and relaxes psychic tension

Of all muscle relaxants in current use, only meprobamate is supported by hundreds of published clinical studies that demonstrate relaxing action on both the brain and the skeletal musculature. EQUANIL reduces muscular spasm and tension, aids in the restoration of mobility, speeds rehabilitation, lessens the emotional overlay.

*Prescribe it in spasm or tension secondary to:* sprains, strains, contractures, fibrositis, myositis, low-back syndrome, frozen shoulder, cervical-rib syndrome, herniated intervertebral disk, wryneck, rheumatoid arthritis, rheumatoid or traumatic spondylitis, certain neuromuscular disorders.

Equanil®

Meprobamate, Wyeth

Wyeth Philadelphia 1, Pa.

of a head covering or floor covering, if such was interposed between the scalp and the cause of the trauma. Sometimes, there may be no external evidence of bruising, and it is revealed only at autopsy.

Impact of the head against some hard surface usually will produce a small irregular laceration, while crushing may cause bilateral bruising. A blow with a blunt instrument can produce a stellate laceration, and a linear object, such as a metal bar, will produce a Y-shaped laceration. Sometimes, knowledge of the nature of the intracranial damage may be essential in order to reconstruct the incident, for lesions in a fixed head will differ considerably from those produced by deceleration impact. The shape of the lacerations may identify the agent which caused the injury, for example, a hammer. Careful exposure and examination of the pericranium or outer table of the skull may confirm the impression gained from the wounds of the scalp. The scalps of children may not be lacerated and may merely show abrasion.

Incised and puncture wounds are due to a sharp edge or a point. The absence of denudation of hair at the edges of the wound or the presence of bridging and of hairs forced into the wound helps differentiate wounds of this type from lacerations. Puncture wounds caused by a sharp point usually will cause similar injuries to the underlying pericranium and bone.

Compound fractures of the skull may cause lacerations of the scalp which may be confused with those resulting from the impact which produced the fracture. Linear fractures will afford evidence of the direction of force, and fractures by contrecoup may occur and must always be considered.

The site of the injury may be significant. The top of the head may be injured when the head butts some object or when a person falls headfirst. However, an injury in this area is usually due to some blow striking the top of the head. The occipital region is commonly injured by falling backward. The character of the skin lesion and fracture and the site of the cerebral lesions will help avoid confusion with blows on the occiput. A bruise of the scalp above and behind the ear in the parietal region with a fissure fracture into the middle fossa commonly is caused by a secondary impact when a person is knocked down by an automobile. Splitting lacerations of the eyebrow, cheek or the lips alone are usually due to a localized impact, such as from a fist or boot. When such lacerations are caused by the face striking the ground, other abrasions on prominent parts of the face will be present. Knuckle-dusters or other hard objects in the hands of an assailant may cause bone injuries which are far more serious than would be expected even from a boot.

*Stage 3*—The next step involves examination of the pericranium and the cranium (outer table). Extensive pericranial hemorrhage (floating scalp) usually is associated with springing of the sutures, but small children, whose scalps are loose, may have an extensive hematoma from relatively little trauma. Occasionally, rupture of the sinus may occur.

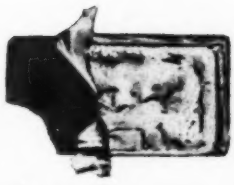
As previously mentioned, the surface of the outer table of the skull may show marks which will identify the weapon. These will coincide with wounds on the scalp. They may be in the form of tangential or vertical cuts, as from a chopper or heavy knife; indentations, as from a hammer; or tangential "egg-top" lesions, caused by impact of the head against an edge. There may be a linear depression, as caused by a cosh, or circular depressions in the case of infants. There may be springing of the sutures with or without fissure, comminuted and depressed fractures. A wound from a beveled projectile is classic.

*Stage 4*—When further information may be obtained from examination of the inner table, the calvaria should be removed. Caution should be taken against indiscreet use of the hammer. An extradural hemorrhage will be obvious, and the dura mater may be tense and on incision reveal an underlying subdural hematoma or severe edema. If the dura mater is ruptured, cerebral herniation will result. A subarachnoid extravasation of blood is usually present, even when there is no obvious cerebral laceration or contusion, but it must be differentiated from congestion. If there is bleeding localized to the base of the brain, an aneurysm always

*(Continued on page A-58)*

*no more battles at vitamin time*

# Delectavites®



## *delectable, chewable, chocolate-like vitamin-mineral nuggets*

No fights, no battles at vitamin time because children love to chew DELECTAVITES. These delectable, easily chewable chocolate nuggets supply all essential vitamins as well as minerals so necessary during the years of growth. As soon as children can chew, they can go directly from vitamin drops to DELECTAVITES. And, *now* you can be sure your little patients will follow your instructions about taking their daily vitamins.

**Each nugget contains:** Vitamin A—5000 Units* / Vitamin D—1000 Units* / Vitamin C—75 mg. / Vitamin E—2 Units† Vitamin $B_1$—2.5 mg. / Vitamin $B_2$—2.5 mg. / Vitamin $B_6$—1 mg. / Vitamin $B_{12}$ Activity—3 mcg. / Panthenol—5 mg. Nicotinamide—20 mg. / Folic Acid—0.1 mg. / Biotin—30 mcg. / Rutin—12 mg. / Calcium Carbonate—125 mg. / Boron—0.1 mg. / Cobalt—0.1 mg. / Fluorine—0.1 mg. / Iodine—0.2 mg. / Magnesium—3.0 mg. / Manganese—1.0 mg. / Molybdenum —1.0 mg. / Potassium—2.5 mg. *U.S.P. UNITS †INT. UNITS

**dosage:** one Delectavites daily. **supply:** Box of 30 (one month's supply), Box of 90 (three months' supply).

WHITE LABORATORIES, INC., KENILWORTH, NEW JERSEY

should be suspected. A chronic subdural hematoma (sometimes bilateral) may be present with old adhesions, although it also may be spontaneous. Sagittal sinus thrombosis always must be considered, for this condition in young children has been mistakenly diagnosed as traumatic contusion.

*Stage 5*—The next procedure requires removal of the brain and examination of the base of the skull before and after stripping of the dura mater. An extradural collection of blood may be found. Extension of fissure fractures in many sites will be easily identified, and some may be traced onto the vault which has been removed. The orbital plates commonly show fractures by contrecoup in occipital deceleration injuries.

*Stage 6*—The surface of the unfixed brain should be examined. After it has been photographed, the brain should be fixed before cutting, by suspension in 10 per cent FORMALIN® saline from the basal arteries, to avoid distortion. The length of time allowed before the brain is cut may have to depend on the urgency of the situation.

At this stage, one should consider the differentiation between trauma and natural disease, especially the possibility of a berry aneurysm which may be on the internal carotid artery. Natural capsular hemorrhages also may rupture onto the surface with subdural hematoma. The sites of contusions and lacerations may be extremely important when differentiating between injuries which occur during deceleration and those of direct impact to a fixed head. Lacerations of the frontal pole with fractures of the occipital bone denote deceleration, and injuries of the occipital pole with fractures of the frontal bone also are usually easy to interpret. The possibility of two independent injuries must be considered, and they should be identified from lesions of the scalp. Uncal and tonsillar herniation will indicate the amount of intracranial tension; but the interpretation of tonsillar herniation should be undertaken cautiously, for postmortem or antemortem posture may be a contributing factor. The amount of flattening of the convolutions may also be of importance.

*Stage 7*—After fixation, the extent and sites

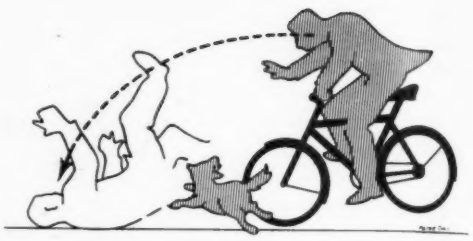


FIGURE 3. Fall from bicycle.

of the brain damage, such as contusion of the falx or damage to the corpus callosum, are determined, and edema is noted. Examination should be made for secondary effects, such as brain stem and midbrain hemorrhage and thrombosis, which invalidate recovery. There should be little difficulty differentiating between these and shear injuries. Old vascular lesions or a deep aneurysm also may be identified. A histologic examination should be made of doubtful lesions.

### *Use of Information*

After collecting the necessary data, the case may be assessed with a view to establishing the following facts: (1) the mechanism of the injury and the nature of the impact, e.g., primary against a rough object, secondary against a rough object, or direct impact by a blunt object, and, if possible, some indication of the type of object; (2) the degree of force and direction of the impact; (3) whether there is more than one injury; and (4) the speed of loss of consciousness, the degree and length of unconsciousness, and the rapidity of death, all of which may help establish how much, if anything, the person could have done after the injury.

### *Case Reports*

The following cases, which have been investigated during the past few years, illustrate some of the aspects previously discussed in the interpretation of head injuries.

*Case 1*—Injury with a blunt instrument—A 44 year old man was alleged to have been struck on the head by a cricket bat wielded by his stepson. Preliminary examination at autop-

*(Continued on page A-60)*

**no asthma symptoms**—Chronic asthmatic patients stay symptom-free with Tedral...the safe, effective, low-cost antiasthmatic designed for prolonged therapy. No single drug can equal Tedral in protecting against bronchial constriction, mucous congestion, and apprehension 'round-the-clock.

Formula: theophylline, ½ gr.; ephedrine, ¾ gr.; phenobarbital, ⅛ gr.
Dosage: 1 or 2 Tedral Tablets q.4.h. plus 1 or 2 Tedral Enteric Coated with the regular dosage at bedtime protect most patients 'round the clock.

**TEDRAL**®

*the dependable antiasthmatic*

WARNER CHILCOTT
MORRIS PLAINS, N.J.

TABLE 1

INCIDENCE OF FRACTURES OF THE BASE OF THE SKULL IN PERSONS EXAMINED AT AUTOPSY AT THE LONDON HOSPITAL MEDICAL COLLEGE, DEPARTMENT OF FORENSIC MEDICINE, 1953-1958

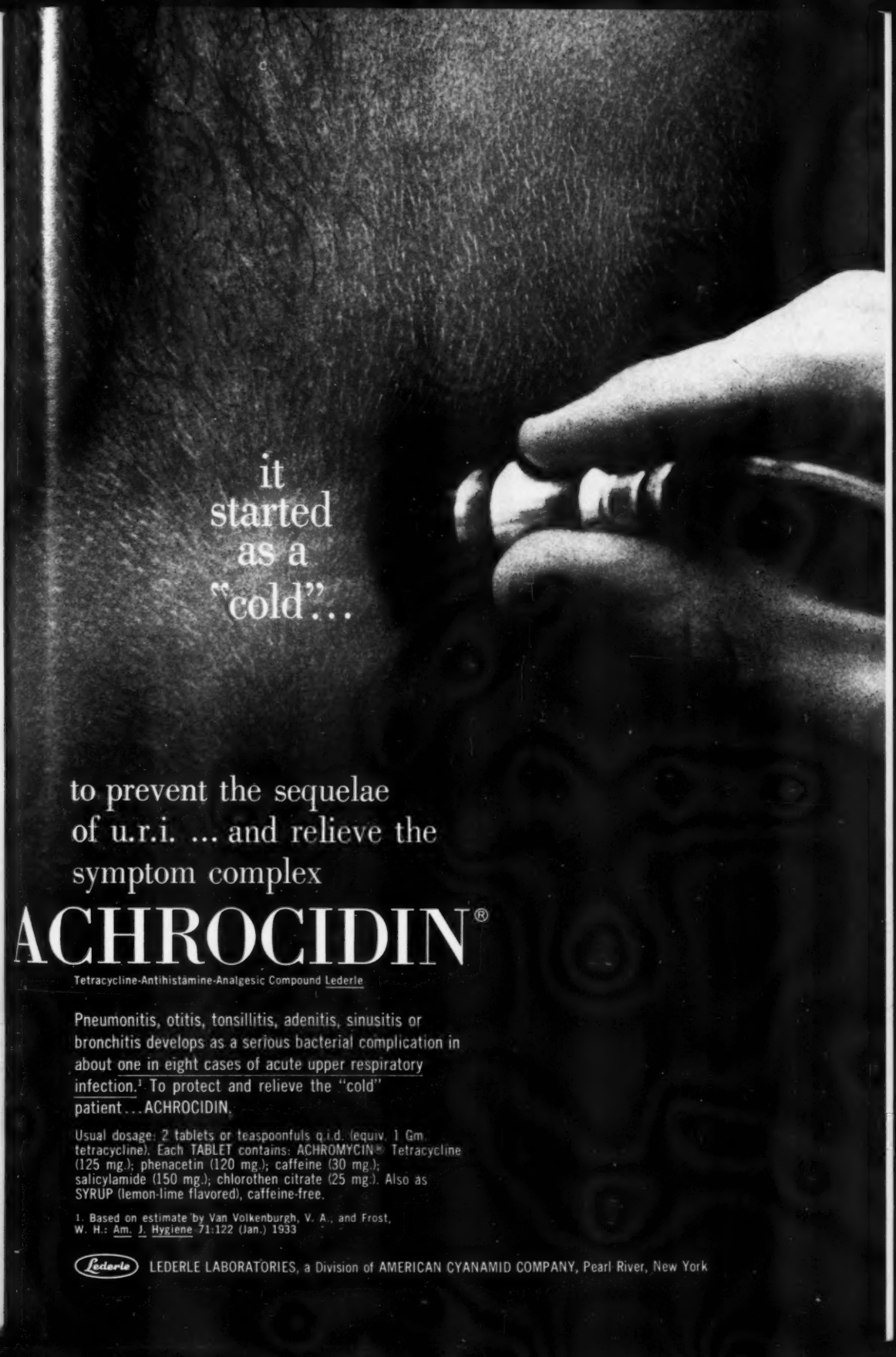
| TYPE OF ACCIDENT | YEAR | SITE OF FRACTURE | | |
|---|---|---|---|---|
| | | *Anterior fossa* | *Middle fossa* | *Posterior fossa* |
| **Pedestrian** | 1953 | 6 | 19 | 5 |
| | 1954 | 3 | 9 | 3 |
| | 1955 | 6 | 17 | 3 |
| | 1956 | 12 | 19 | 8 |
| | 1957 | 1 | 4 | 2 |
| | 1958 | 6 | 15 | 4 |
| **Falls** | 1953 | 5 | 5 | 2 |
| | 1954 | – | 1 | – |
| | 1955 | – | | 2 |
| | 1956 | 2 | 3 | 3 |
| | 1957 | | 2 | 3 |
| | 1958 | 4 | 9 | 9 |
| **Motorcycle** | 1953 | 5 | 9 | 2 |
| | 1954 | 6 | 4 | – |
| | 1955 | 2 | 6 | 1 |
| | 1956 | 5 | 10 | 4 |
| | 1957 | 6 | 8 | 3 |
| | 1958 | 2 | 7 | 3 |
| **Pedal cycle** | 1953 | – | 3 | 1 |
| | 1954 | 1 | 5 | 4 |
| | 1955 | 1 | 6 | 1 |
| | 1956 | – | 3 | 4 |
| | 1957 | 5 | 7 | 2 |
| | 1958 | 1 | | 1 |
| **Motor vehicle** | 1953 | | – | 1 |
| | 1954 | – | 2 | – |
| | 1955 | – | 1 | – |
| | 1956 | 3 | 2 | 2 |
| | 1957 | 4 | 2 | – |
| | 1958 | 3 | 5 | 3 |
| **Miscellaneous** | 1953 | 9 | 29 | 5 |
| | 1954 | 8 | 18 | 13 |
| | 1955 | 5 | 22 | 6 |
| | 1956 | 8 | 16 | 5 |
| | 1957 | 5 | 17 | 3 |
| | 1958 | 7 | 15 | 3 |

sy showed very little external injury to the scalp. However, bruises on the forearms and hands showed abrasion patterns that could have been caused by the binding of a cricket bat. Reflection of the scalp revealed extensive comminuted fractures of the vault of the skull on the right side, localized trauma below the fractures, and subarachnoid and subdural hemorrhage.

It was concluded that the injuries to the skull were consistent with direct impact by some blunt instrument with a fairly broad surface. Although the injuries to the skull and scalp did not prove that the alleged weapon had been used, the injuries to the arms were typical defense injuries and showed marks similar to those which would be produced by the bat.

*Case 2*—Injury to a fixed head by a blunt instrument—A 42 year old man formed an association with a prostitute without knowledge

*(Continued on page A-62)*




to prevent the sequelae of u.r.i. ... and relieve the symptom complex

# ACHROCIDIN®

Tetracycline-Antihistamine-Analgesic Compound Lederle

Pneumonitis, otitis, tonsillitis, adenitis, sinusitis or bronchitis develops as a serious bacterial complication in about one in eight cases of acute upper respiratory infection.[1] To protect and relieve the "cold" patient... ACHROCIDIN.

Usual dosage: 2 tablets or teaspoonfuls q.i.d. (equiv. 1 Gm. tetracycline). Each TABLET contains: ACHROMYCIN® Tetracycline (125 mg.); phenacetin (120 mg.); caffeine (30 mg.); salicylamide (150 mg.); chlorothen citrate (25 mg.). Also as SYRUP (lemon-lime flavored), caffeine-free.

1. Based on estimate by Van Volkenburgh, V. A., and Frost, W. H.: Am. J. Hygiene 71:122 (Jan.) 1933

Lederle LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

TABLE 2

SITE OF FRACTURES OF THE SKULL IN PERSONS EXAMINED AT AUTOPSY AT THE LONDON HOSPITAL MEDICAL COLLEGE, DEPARTMENT OF FORENSIC MEDICINE, 1953-1958

| SITE | 1953 | | 1954 | | 1955 | | 1956 | | 1957 | | 1958 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Cases* | *Per cent* | *Cases* | *Per cent* | *Cases* | *Per cent* | *Cases* | *Per cent* | *Cases* | *Per cent* | *Cases* | *Per cent* |
| Anterior fossa | 25 | 19.9 | 18 | 19.4 | 14 | 15.7 | 30 | 21.9 | 21 | 23.8 | 23 | 19.3 |
| Middle fossa | 65 | 51.5 | 39 | 42.0 | 52 | 58.5 | 53 | 38.7 | 40 | 45.5 | 51 | 42.8 |
| Posterior fossa | 16 | 12.7 | 20 | 21.5 | 13 | 14.6 | 26 | 19.0 | 13 | 14.8 | 23 | 19.3 |
| Posterior and middle fossae | 10 | 7.9 | 9 | 9.7 | 5 | 5.6 | 10 | 7.3 | 4 | 4.5 | 9 | 7.6 |
| Anterior and middle fossae | 10 | 7.9 | 7 | 7.5 | 5 | 5.6 | 18 | 13.1 | 10 | 11.4 | 13 | 10.9 |
| TOTAL | 126 | | 93 | | 89 | | 137 | | 88 | | 119 | |

of her profession. Later, he became disillusioned, and in a fit of jealousy or revenge stabbed the girl in the back. He then fled, but was pursued by her friends who eventually tripped him. During the ensuing proceedings, he received head injuries believed to have been caused by a piece of concrete. He was taken to hospital where he underwent a craniotomy and removal of part of a comminuted depressed fracture at the back of the skull. He subsequently died. Examination at autopsy showed that in addition to the injury caused by striking the ground, the opposite parts of the skull had been injured without contrecoup. This indicated that the man had sustained injuries from impact to the fixed head. The injuries were consistent with the head having been struck while on the ground by some heavy object, such as a piece of concrete.

*Case 3*—Tangential injury to the skull—While playing on the ropes of a gymnasium, a 14 year old boy fell on his head and was temporarily stunned. He was taken to hospital at 8:30 P.M. and remained there for an hour, during which period he was fully conscious. Roentgenographic examination did not reveal a fracture. He went to bed at 10:30 P.M. and was found dead at 7:55 A.M.

At autopsy the pupils were equal and half dilated. No external injury of the scalp was visible, but reflection of the scalp showed a fracture running into the right middle fossa and involving the middle meningeal artery. There were a large extradural hematoma, flattening of the brain, and slight local contusion. No secondary pontine hemorrhage was noted. There had been respiratory failure with gross pulmonary edema.

The injuries were typical of a fall on the head without deceleration. The case followed the classic history of an extradural hemorrhage and exemplified the importance of keeping patients with this type of history under observation for the first 24 hours.

*Case 4*—A deceleration injury—A 62 year old man was admitted to hospital after falling from his bicycle (figure 3). He was unconscious and was transferred to a neurosurgical unit where parietal burr holes were made and 30 cc. of subdural clot was evacuated from over both hemispheres. This caused some improvement in the level of consciousness. Roentgenograms of the skull and chest showed an oblique linear fracture through the parietal and squamous temporal regions on the left side and fracture of the second, third and fourth ribs also on the left side. The patient died 10 days after the injury.

Findings at autopsy were: (1) an abraded bruise in the left temporal region; (2) a linear fracture reaching into the left middle fossa; (3) contusions of the left and right temporal and right frontal lobes with edema and necrosis; and (4) pulmonary embolism due to bilateral phlebothrombosis of the veins of the

*(Continued on page A-64)*

# breakfast on the run... lunch on the job... time for

# Myadec®

high potency vitamin-mineral formula

When dietary habits are poor, MYADEC helps prevent vitamin-mineral deficiencies by providing comprehensive nutritional supplementation. Just one capsule daily supplies therapeutic doses of nine important vitamins plus significant quantities of eleven essential minerals and trace elements.

Each MYADEC Capsule contains:

| | |
|---|---|
| **VITAMINS:** | |
| Vitamin $B_{12}$ crystalline | 5 mcg. |
| Vitamin $B_2$ (riboflavin) | 10 mg. |
| Vitamin $B_6$ (pyridoxine hydrochloride) | 2 mg. |
| Vitamin $B_1$ mononitrate | 10 mg. |
| Nicotinamide (niacinamide) | 100 mg. |
| Vitamin C (ascorbic acid) | 150 mg. |
| Vitamin A (7.5 mg.) | 25,000 units |
| Vitamin D (25 mcg.) | 1,000 units |
| Vitamin E (d-alpha-tocopheryl-acetate concentrate) | 5 I.U |
| **MINERALS** (as inorganic salts): | |
| Iodine | 0.15 mg. |
| Manganese | 1.0 mg. |
| Cobalt | 0.1 mg. |
| Potassium | 5.0 mg. |
| Molybdenum | 0.2 mg. |
| Iron | 15.0 mg. |
| Copper | 1.0 mg. |
| Zinc | 1.5 mg. |
| Magnesium | 6.0 mg. |
| Calcium | 105.0 mg. |
| Phosphorus | 80.0 mg. |

Bottles of 30, 100, 250, and 1,000.

PARKE, DAVIS & COMPANY
DETROIT 32, MICHIGAN

90359

FROM "TENSE AND ANXIOUS"
TO

"CALM
AND
CONFIDENT"

WITH

BUTISOL sodium®

butabarbital sodium

BUTISOL reduces nervous tension without producing apathy or mental confusion.

Tablets,
Repeat-Action Tablets,
Elixir, Capsules

DOSAGE: 15 to 30 mg. three or four times a day.

McNEIL LABORATORIES, INC.
Philadelphia 32, Pa.

McNEIL



calves. These injuries are typical of deceleration injuries due to a fall on the side of the head. Such injuries are very common in people knocked down by automobiles. The terminal pulmonary embolus is a common complication of head injury.

This last case draws attention to the relatively high incidence in England of fractures of the middle fossa resulting from automobile accidents. Tables 1 and 2 show the results of head injuries found at autopsies carried out by the Department of Forensic Medicine at The London Hospital Medical College during 1953 to 1958, inclusive. It will be noted that fracture of the middle fossa occurs more frequently than does fracture of the posterior or the anterior fossa. This conforms with findings in England where head-on impacts, except by drivers of motorcycles, are less common than in North America, and where more pedestrians are killed in accidents involving motor vehicles than are drivers.

### *Summary*

The procedure outlined here for the routine examination of persons who die from head injuries complies with the Coroner's Rules (1953), which state that the material on which the cause of death is based shall be retained after autopsy. The use of photographs and the retention of the brain for fixation before the final dissection make it possible to refer to previous cases and their interpretation and provide an opportunity for representatives of interested parties in both civil and criminal cases to see the material.

### ACKNOWLEDGMENT

I should like to record my appreciation to the various coroners and clinicians who have allowed me to use their material and records, to S. A. Day and A. J. Hardy, who have been responsible for the photographs and preparation of the material, and to Mrs. E. Sanders, who prepared the statistical evidence from our punch card records.

### REFERENCE

CAMPS, F. E.: The mechanism of head injuries; a method of record and presentation from the clinical, pathological and medico-legal aspects. Proc. Second Internat. Cong. Neuropath. 2:469-472, 1955.

# Radiology FOR PRACTICING PHYSICIANS

PAUL C. HODGES*

## Pulmonary Histoplasmosis

PAUL C. HODGES*

### *Nature of the Infection*

It has been more than half a century since Darling described a rare, fatal disease caused by an organism he named *Histoplasma capsulatum*. Only within the past 14 years have milder, more prevalent forms of the disease been recognized. Effective drug therapy is a most recent development.

In infected men or animals, the organism is in the yeast phase and cannot be transmitted to others, but in the soil and on suitable artificial media it develops mycelium and spores. The spores are so infectious that mycologists working with histoplasmosis almost invariably acquire the disease.

Natural infections frequently are found to date from exposure to soil or partly decomposed vegetable material, particularly in locations that are damp and are contaminated by bird droppings. The geographical range of the spores is much wider than was first supposed.

*Emeritus Professor and Chairman, Department of Radiology, University of Chicago, Chicago, Illinois.

### *Clinical Course*

Frequently, the symptoms of the active phase of histoplasmosis are so mild that they are unnoticed or at least forgotten by the patient by the time skin testing or routine x-ray examination reveals that there has been an infection. Occasionally, one sees a patient who has a brief unidentified illness characterized by cough, fever, malaise and bilateral pulmonary lesions resembling transient mild bronchopneumonia and followed some months later by solitary or multiple calcified nodules in the parenchyma of the lung, calcification of the hilar glands, and a positive histoplasmin skin test. Less frequently, the disease progresses rapidly or sometimes slowly to the development of one or more large granulomas in the hilus or parenchyma or to cavitation and fibrosis. Fortunately, the fatal generalized form is

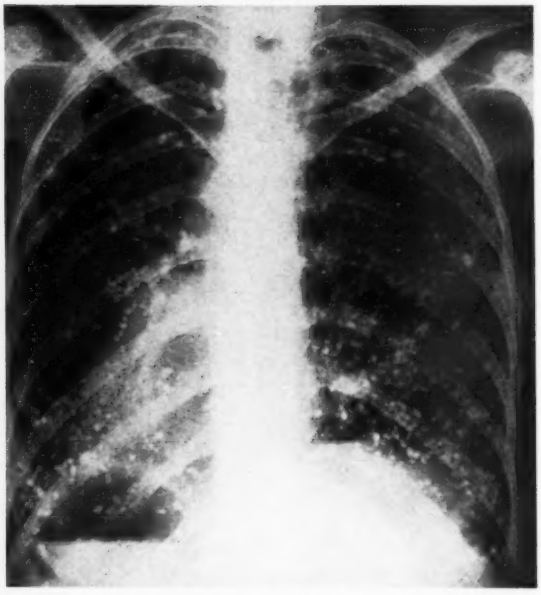


FIGURE 1. Disseminated calcified histoplasmosis. At the onset of disease, 10 years before this film was made, the lesions were described as "soft." Calcification began within a year and has remained stationary for several years. The patient is severely emaciated and has a productive cough; sputum is negative for tubercle bacilli and *H. capsulatum*. This is a spectacular grade of involvement; it has impaired the patient's health, and there probably are similar lesions in the abdominal viscera.

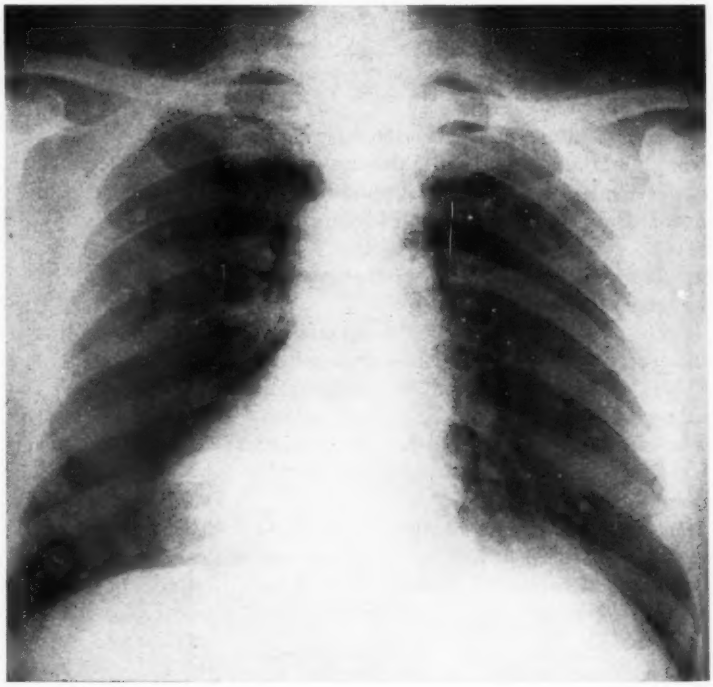


FIGURE 2. Multiple calcified nodules of histoplasmosis. The x-ray diagnosis in this case was pulmonary histoplasmosis and osteochondroma at the anterior end of the first rib on the left side. The patient died two years later from coronary infarct; at autopsy, both diagnoses were confirmed.

Soft lesions such as these formerly were misdiagnosed as calcified miliary tuberculosis. With the aid of the histoplasmin skin test, biopsies and autopsies, this pattern has been established as commonplace for histoplasmosis and is seldom, if ever, seen in tuberculosis.

rare. In the one case which I saw, diagnosis was not established until autopsy.

### *X-ray Diagnosis*

*Multiple calcified parenchymal nodules*—In the 1940s, as the new knowledge of histoplasmosis was developing, the most prevalent form seemed to be multiple calcified parenchymal nodules. Previously, radiologists and pathologists had misdiagnosed these as miliary tuberculosis, but a high correlation between such lesions, a negative tuberculin test, and a positive histoplasmin test established their nontuberculous nature. In retrospect, it is hard to defend the old error, because it is doubtful that miliary tuberculosis ever subsides and leaves the sort of calcified parenchymal nodules that are commonplace in histoplasmosis.

*Solitary parenchymal nodule with hilar gland involvement*—Whereas most, if not all, of the supposed "calcified miliary tuberculosis" has proved to be histoplasmosis, it is currently believed that only a part of the calcified primary complex with regional lymph gland

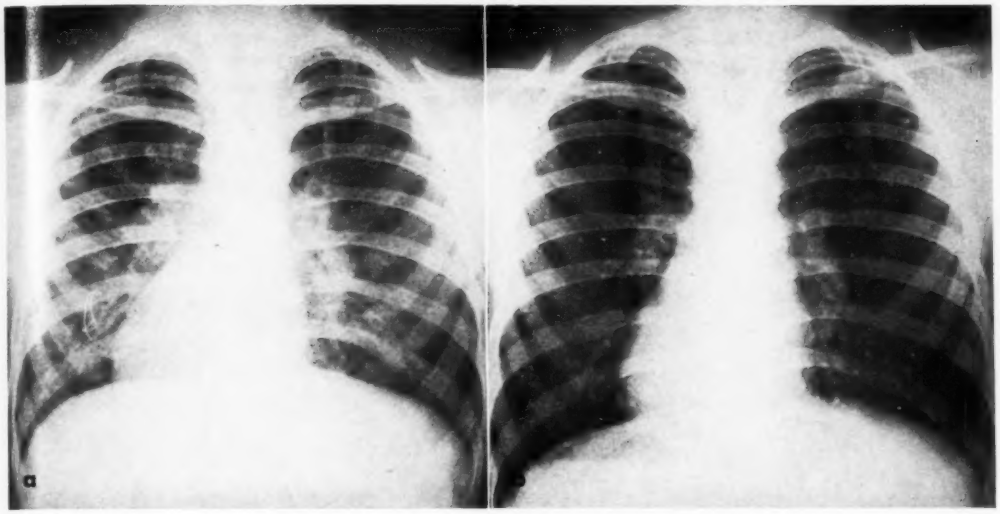


FIGURE 3a. Multiple nodules of histoplasmosis before calcification. Six weeks after onset of fever and malaise, this patient was free of symptoms. Taken at that time, this chest film showed bilateral splotchy parenchymal lesions and enlargement of the hilar glands. Within six months, calcification had begun.

b. Two years after onset, calcification was complete; there has been no significant subsequent change.

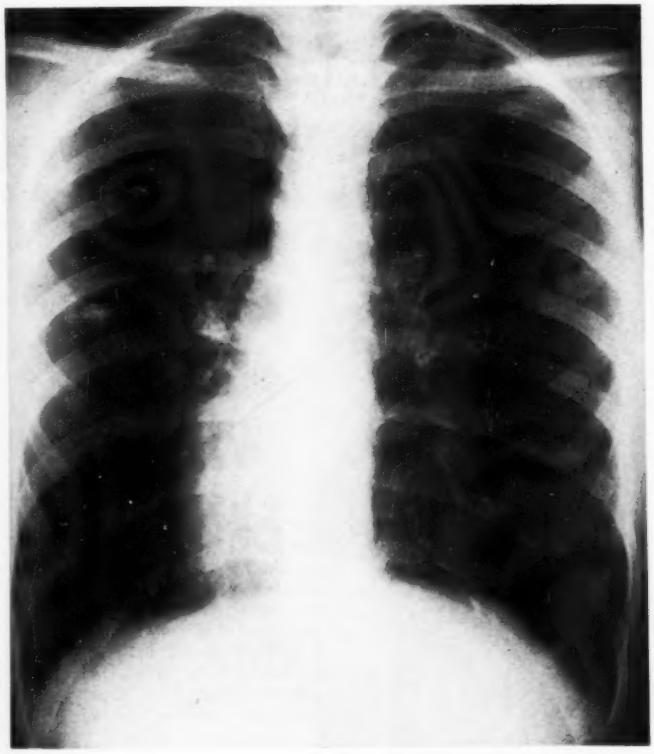


FIGURE 4. Solitary calcified primary complex. In this patient, the tuberculin skin test was negative (1/1000); the histoplasmin skin test was positive (1/100), and the histoplasmosis complement fixation test was negative. Five years earlier, the roentgenographic appearance was about the same as in this film.

Unlike the multiple nodules illustrated in figures 1 and 2, a solitary nodule may indicate either tuberculosis or histoplasmosis; x-ray examination will not distinguish between the two.

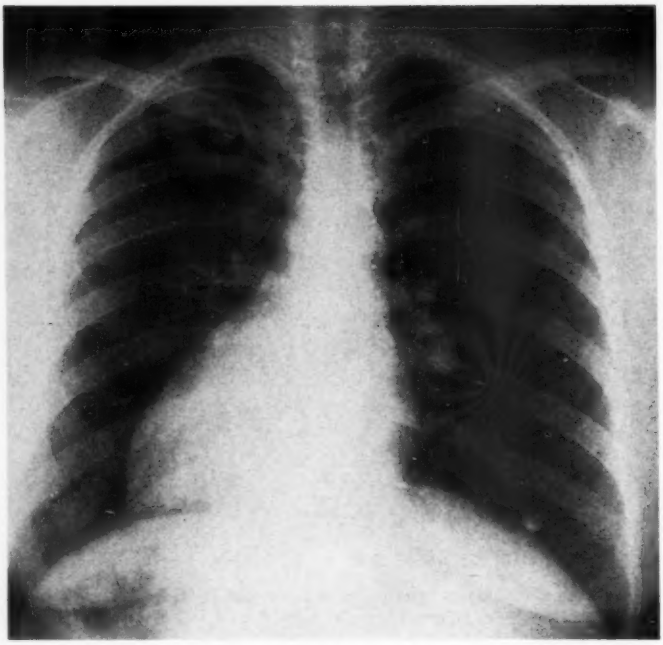


FIGURE 5. Solitary calcified primary complex which is known to be not more than five years old. Five years before this film was made and during the course of a brief respiratory disease, x-ray examination showed the lungs to be clear. Six months later, a nodule was found in the right base, with enlargement of the right hilar glands. Both lesions soon began to calcify; the appearance has been stable for several years.

FIGURE 6. Circumscribed nodules of histoplasmosis which were mistaken for neoplasm. Asymptomatic nodules discovered at routine x-ray examination 18 months earlier are unchanged in this film. The fact that there are two nodules located at the axillary aspect of the lung argues against neoplasm and for histoplasmosis; furthermore, the skin test for histoplasmin was positive. In spite of this, surgical resection was done; microscopic examination confirmed the diagnosis of histoplasmosis.

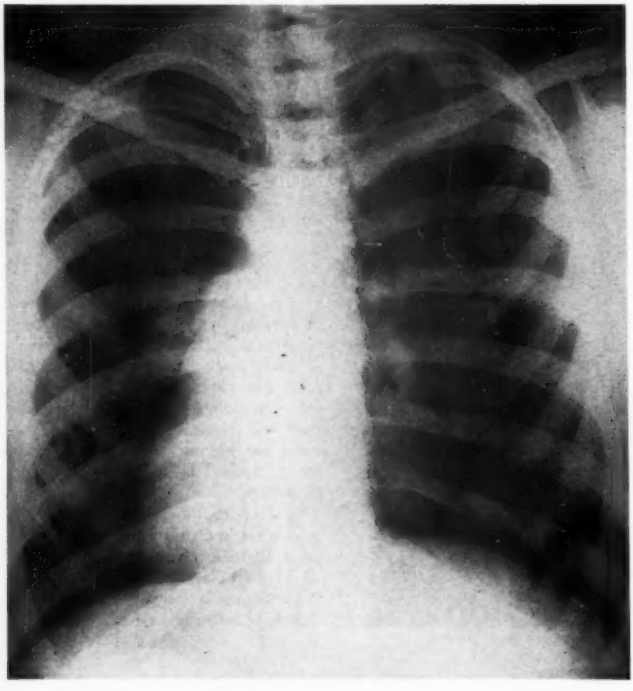


FIGURE 7. Solitary histoplasmosis granuloma simulating metastasis from sarcoma. The lesion in the left hilus looks like a granuloma, and the histoplasmin test in this patient gave positive results; however, because the patient had a testicular tumor which proved to be a rhabdomyosarcoma, it was feared that the hilar lesion might be a metastasis. Biopsy material obtained at exploratory thoracotomy showed the lesion to be histoplasmosis.

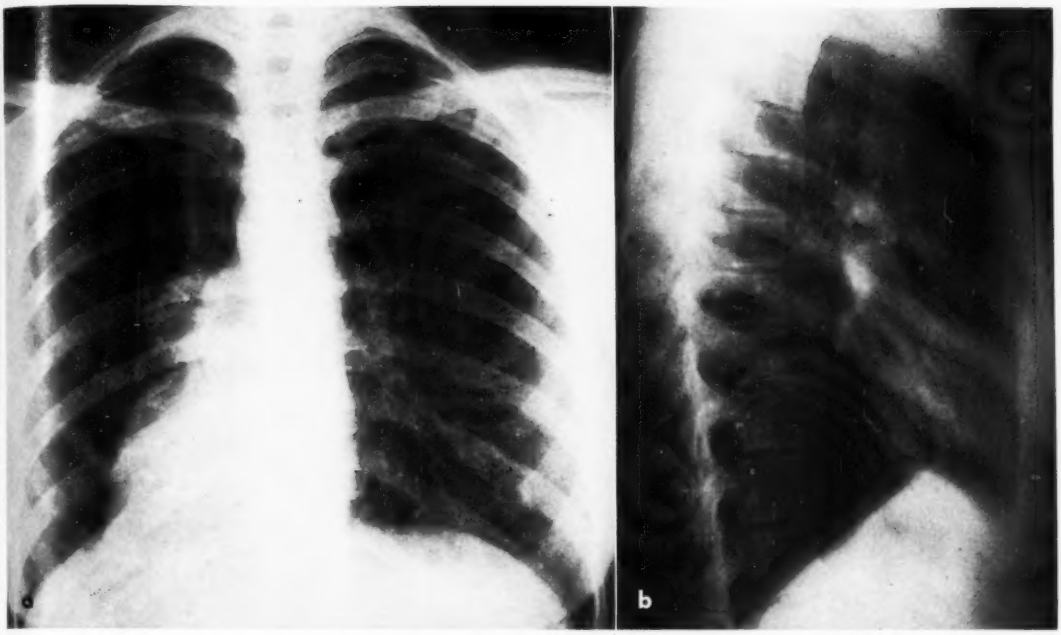



FIGURE 8. Histoplasmosis granulomas mistaken for a vascular anomaly.

a. Frontal view showing 3 by 4 cm. mass in the left hilus and a 1 cm. mass at the cardiac border at about the auriculoventricular junction. Radiologic diagnosis: granuloma.

b. Left lateral view in which a third mass, measuring 1.5 cm. in diameter, can be seen behind the larger hilar mass. In spite of these findings, a positive histoplasmin test and a negative angiocardiogram, the thorax was explored and the smallest of the three masses was removed for biopsy. Histologic diagnosis: histoplasmosis granuloma.

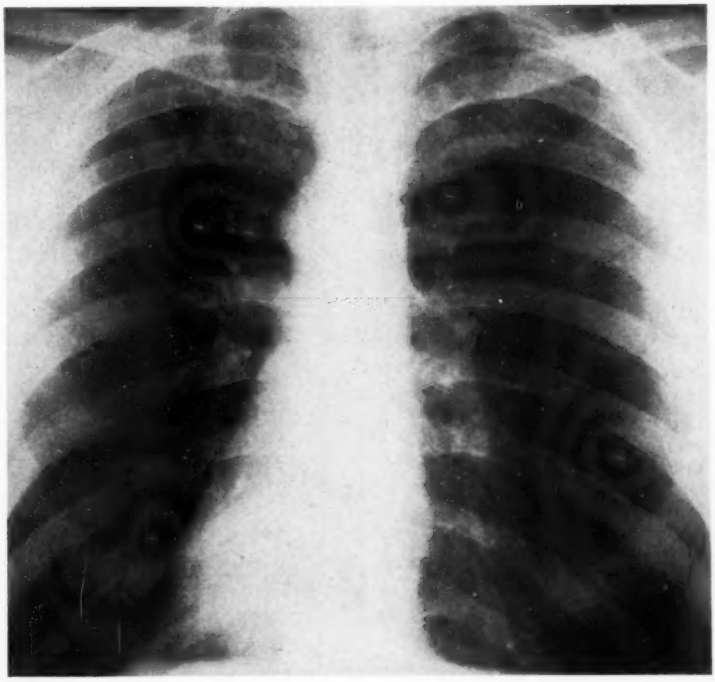


FIGURE 9. Acute active cavitary histoplasmosis. A 1.5 by 2.5 cm. cavity is seen in the apex of the left lung. The lesion is almost exclusively destructive, with little evidence of repair. *H. capsulatum* was cultured from the sputum. Clinical cure followed lobectomy.

FIGURE 10. Chronic fibroplastic cavitary histoplasmosis. This patient had pulmonary symptoms for five years. Although he had been admitted to several sanatoriums, tubercle bacilli had never been found in the sputum. Six months before this x-ray was made, *H. capsulatum* was recovered from the sputum. Following lobectomy, the course was stormy, and the patient died on the twenty-fourth postoperative day. Autopsy showed histoplasmosis of the pleura, the remaining two right lobes, and the left upper lobe, with miliary histoplasmosis of the liver and kidneys.

FIGURE 11. Chronic fibroplastic cavitary histoplasmosis. This patient had a 39 year history of intermittent hemoptysis. Obviously old lesions are seen at the right apex, with cavitation, pleural thickening and retraction of the trachea and right hilus toward the lesion. Clinical cure followed lobectomy.

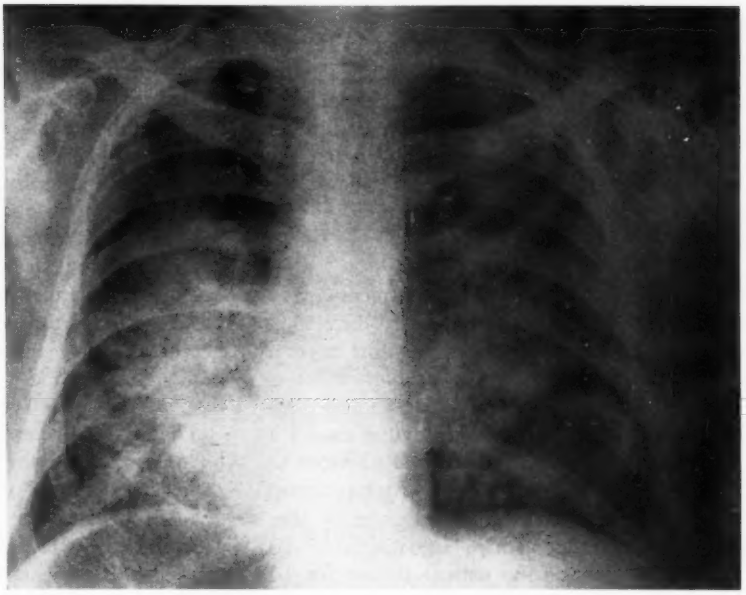


FIGURE 12. Fatal generalized histoplasmosis (so-called cytomycosis). While this patient was alive, the lesions in the lung were assumed to be uremic infiltration. Autopsy revealed spectacular, unsuspected generalized histoplasmosis involving the lungs, spleen, liver, kidneys and the reticuloendothelial system.

involvement is histoplasmosis rather than tuberculosis. The distinction cannot be made radiologically; it must be determined by immune reactions.

*Solitary or multiple large granulomas*—Pathologists have pointed out that the granuloma of histoplasmosis matures early. Thus, if in a particular case it can be established that a well-circumscribed, dense, but only slightly calcified granuloma is of rather recent origin, histoplasmosis is a more likely diagnosis than is tuberculosis.

*Fibrocaseous histoplasmosis*—Even in tuberculosis, the concept of a "primary" versus a "reinfection" type of lesion rises and falls in popularity. Recent reports on United States Navy personnel favor the idea that so-called reinfectious types of lesions are, in fact, reactivations of pre-existing foci. In histoplasmosis, on the contrary, experimental evidence indicates strongly that after a primary lesion has healed and the skin test has become positive reinfection fails even after inoculation with massive doses of spores of known virulence. For these reasons I, with many others, prefer for both diseases the term "fibrocaseous" for lesions which some might call "reinfection." In this stage, the two diseases are radiologically indistinguishable; fortunately, however, there usually is sputum present from which one can recover either tubercle bacilli or *H. çapsulatum*.

### *Immunology*

The histoplasmin skin test is a most important clinical tool. Although there is some cross reaction with other fungi, only in histoplasmosis will the reaction be of standard severity. A complement fixation test is available, but it is difficult to obtain and maintain a potent antigen or a quantitative response to a standard dose. The test is most useful in active disease before the skin test shows positive results. In such cases, it should be repeated frequently; an increased response with the progress of the disease is strongly indicative of the diagnosis of histoplasmosis.

### *Histology*

The pathologist helps most when he is supplied fresh material which on culture yields characteristic spores. On direct examination of active lesions, he searches for the minute intracellular bodies which are the yeast phase

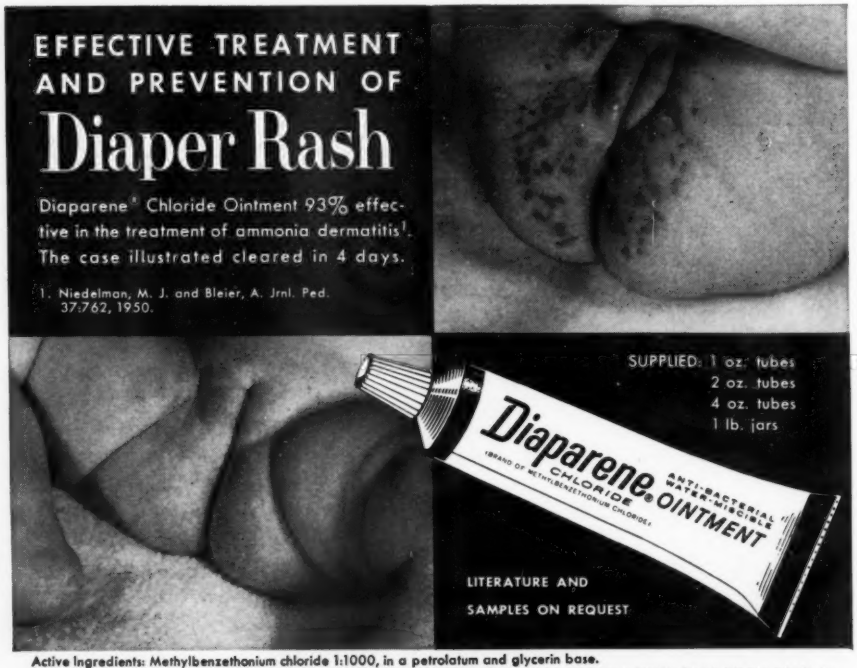
of the organism. Usually, these are present in great quantities, and they stain bright red by the Gridley fungus stain. This stain is more difficult to use in the presence of old calcified nodules in which bits of calcium and other debris may take the stain and to all but the expert eye simulate the polysaccharide of the capsule of *H. capsulatum*.

### *Therapy*

*Drugs*—After many disappointments, very recently an antibiotic has been developed which is reasonably effective against several of the fungi, including *H. capsulatum*. It is known as amphotericin B. At least in its present form, the drug is so toxic that it causes a reversible elevation of blood urea nitrogen to as much as 40 or 60 and a rise of temperature to from 101 to 102° F. It is best given by continuous intravenous drip, injecting for 10 hours and allowing the patient to rest for 14 hours. The treatment should be continued for several weeks. Obviously, this treatment requires that the patient be confined to a hospital and supervised by experts; it is used principally to prepare patients who are scheduled for surgery.

*Surgery*—Because the patient who harbors a large tuberculous granuloma runs the constant risk of reactivation, he is well advised to have the lesion extirpated surgically. In histoplasmosis, on the other hand, reactivation occurs seldom if ever, and surgery therefore is contraindicated. In both diseases, active fibrocaseous lesions, particularly with cavities, are best resected. Now, in histoplasmosis as in tuberculosis, surgery can be rendered easier, more effective and vastly safer by preoperative and postoperative drug therapy.

The surgical removal of arrested lesions of histoplasmosis on the theory that they may be neoplasms or vascular anomalies is to be avoided, because the late sequela of lung surgery may be worse than even a pulmonary neoplasm and because meticulous attention to all of the diagnostic data usually will establish the correct diagnosis without recourse to surgical exploration.


EFFECTIVE TREATMENT
AND PREVENTION OF
Diaper Rash
Diaparene® Chloride Ointment 93% effective in the treatment of ammonia dermatitis[1]. The case illustrated cleared in 4 days.
1. Niedelman, M. J. and Bleier, A. Jrnl. Ped. 37:762, 1950.
SUPPLIED: 1 oz. tubes
2 oz. tubes
4 oz. tubes
1 lb. jars
Diaparene® CHLORIDE OINTMENT
ANTI-BACTERIAL WATER-MISCIBLE
LITERATURE AND
SAMPLES ON REQUEST
Active Ingredients: Methylbenzethonium chloride 1:1000, in a petrolatum and glycerin base.
HOMEMAKERS PRODUCTS DIVISION • GEORGE A. BREON & CO., 1450 BROADWAY, NEW YORK 18, N. Y.

# Through the Stethoscope

WENDELL J. S. KRIEG

## Letters to a Medical Student

*My dear son:*

From my past letters you may have gained the impression that all your work will be research and creative writing, and that they are all that matter. Teaching and preparation will take fully half your time. Daily contact with your students and their reactions will be rather immediate spurs to do this as well as you can. It took me years to realize finally that the material one presents in teaching has no relation to one's thinking and does not evolve as one progresses with one's work. You are there to transmit with clarity and exactness an established body of knowledge. You can by no means present the entire corpus or the finer points in any routine course, no matter how fascinated you may be with them or how thoroughly you may have mastered them.

There is a great difference between being a professor in a college and holding the same position in a medical or other professional school; there is more difference between teaching the humanities and teaching the sciences. The college professor has more latitude in what he selects to teach; he even creates courses to incorporate his interests. The medical professor has a body of subject matter which must be transmitted exactly, as a groundwork for future courses; he has little opportunity for electives or didactic graduate courses.

Thus, a medical professor who has spent half his working days in research finds himself at 60 teaching the same course he taught at 35, without any opportunity to branch out or to give the students the benefit of his increased knowledge. Frequently, medical students never learn to what subject their professor has devoted his best hours. In fact, we are retrogressing, for such substantial cuts have been taken in the time scheduled for the preclinical sciences that only the essentials can be taught. Simultaneously, with the great opportunities for financing medical research from outside sources and with year-round research assistants, the professor feels obliged to maintain a year-round and often extensive research program.

The solution of this quandary is simple. We have only to interpret the titles of the various ranks more literally. The full professor professes; the assistant professor assists the professor; the associate professor is his close associate; the instructor does the instructing.

*(Continued on page A-112)*

Therefore, a full professor does the over-all planning, gives a selection of the lectures, and maintains standards. The other professorial personnel set and mark the examinations and handle details. The professor teaches the teachers; mastery of the subject by new men is not just assumed. They then edit the professor's teaching and adapt it to the students' level without the professor's interference.

The course can even be given on a pass or honors system. The pass students are held responsible for mastering the required material. The honors students have more latitude; perhaps they write a term paper, and they are taught largely by the professor himself. To insure that there will be honors candidates, it should be made clear that the grade of *A* is awarded only to honors students. Thus gifted or interested students are granted what they really need most, and the timeservers are rescued from the professor—and the professor from them!

If our country is to continue as a world leader in education (I have no worries about the Russians), we should establish a university entirely on the graduate level, preferably in Washington because of the great library resources there. It would be staffed by leaders in the respective subjects, who would be saved from undergraduate instruction. In the U. of A. (University of America) all courses would be at the graduate level, and all research facilities would be financed by national taxes.

When you are lecturing to medical students, never stray from the subject matter of the course you are hired to teach. The students don't want it; they will pay no attention to it, and they will come to dislike you for doing it. If you imagine that you are the apostle of culture, the harbinger of the higher viewpoint, and that you should give them the fruits of your broader education, suppress it. Don't preach to them; don't encourage them in anything but the course work itself. The medical student doesn't want any more culture; he doesn't want philosophy; he wants only medicine, and this seems enough to monopolize his attention. Don't talk to students of your experiences or your ideas; they only hold it against you. Don't entertain them with stories or informal badinage; they may seem entertained, which may egg you on, but they apparently resent it afterward. Even with subject matter, don't take flights of inspiration. It just frustrates and annoys them. Go along slowly and logically in a systematic manner, always giving them facts. List your points; categorize them. Don't give your students too much—only what they are "responsible for," as they like to put it. A medical school lecture is a highly artificial procedure for one who wants to be an educator in the broader sense, so give up any prospects of becoming such.

There is no use in trying to oppose this situation and saying, "Therein lies my crusade." You only batter your head against a stone wall. You can really injure yourself and gain the antagonism of the students. They don't want clever persons, fancy pants, prima donnas, artists or prophets. They are very young, very busy and somewhat frightened; they want security and freedom from fear. The best you can be is a *pauper dei* of science. If you can go around looking humble and meek and behave in a self-depreciatory manner, no one will criticize you. If you can't, you will just have to take the consequences.

It goes even further than that; these strictures extend to the faculty, and I am ashamed to say it. Keep free of frills, and don't expect to discuss extracurricular subjects such as art, travel, literature, women or hobbies with any but the rare proved kindred spirit.

As long as you are teaching, you will not be happy without gaining the affection of your students. This will probably come naturally, as they are anxious to have someone on whom to lean. If you don't fall into it naturally, you will have to buy it. You buy it with concessions on subject matter, itemization of points, examinations of the type expected, and clinical applications. Yet you can't let the students tell you how or what to teach. You are supposed to know more than they; that is why you are paid and they are paying. One man transformed an inspiring textbook into a mediocrity when he let his son, who had become a medical student, tell him how to revise it. Erasmus said long ago that the first step in learning is love of the teacher, and it is as true today as it was in the sixteenth century. Love of the subject is a corollary to this. I used to do my best work in a subject when I imagined while taking the course that I was going to specialize in it, and I recall that I was pretty fickle.

Teaching enables you to go over the sub-

*(Continued on page A-114)*

# Many Uses for This Compact GOMCO Aspirating Pump

## GOMCO No. 789 PORTABLE ASPIRATING PUMP

Like all Gomco equipment, the 789 is quality-built for years of trouble-free service. It is easy to clean, very simple to operate and requires a minimum of maintenance.

The lightweight Gomco No. 789 Aspirating Pump is saving valuable time and energy in thousands of hospitals and clinics from coast to coast. Weighing only 16 pounds, it is easily carried wherever the need arises.

The many important uses of the 789 include general post-operative work, removal of mucous from throats of new-born and for polio cases.

Accurate regulator valve and gauge provide precision control of suction from 0″ to 20″ of mercury. The exclusive, patented Gomco Safety Overflow Valve prevents pump damage by closing the suction system upon entry of moisture into the valve. Rubber-tired mobile stands are available if desired.

Ask your Gomco dealer to show you the many advantages of the 789 Aspirating Pump. He will be glad to demonstrate this and any of the other Gomco units in which you may be interested.

**GOMCO SURGICAL MANUFACTURING CORP.**

**846-M E. Ferry St., Buffalo 11, New York**

Distributed Outside the U. S. A. and Canada by: **INTERNATIONAL GENERAL ELECTRIC CO., 150 E. 42nd St., New York 17, N. Y.**

ject matter every year and prevents your becoming too narrow. Students' questions taken cumulatively are searching and stimulating; interested students are an inspiration, and graduate students are a rock and a fortress.

Although you won't be concerned with graduate students for a time, when you do have them remember that they are *la crème de la crème* and that their minds are a solemn trust. If you assign them a problem which is simply a corner of what you are doing and which you don't want to bother to work out, you may not be helping them develop in the best way. It is much better for a graduate student to be working on a problem *he* thought of and for you to help him as you can. In fact, if he doesn't have a specific interest, you can well wonder why he wanted to take an advanced degree in the first place. Although he may be a nuisance, the boy who knows what he wants to do will probably go further and ultimately will reflect more credit on you. The counterpart of this is true, too, so realize that you are a rather important person in your master's life, and try to fulfill his expectations.

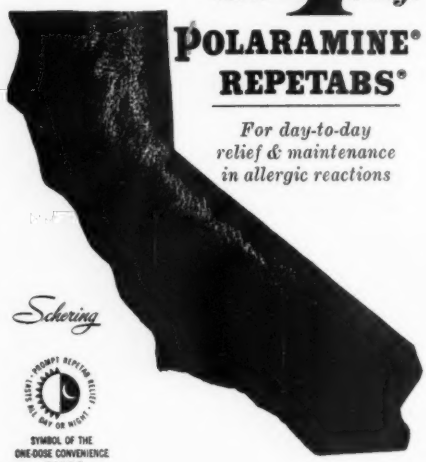
*And so, good night,*
*Father*


*wherever the 4 winds blow*

*new 4 mg.*

POLARAMINE® REPETABS®

*For day-to-day relief & maintenance in allergic reactions*



Schering

SYMBOL OF THE ONE-DOSE CONVENIENCE YOU WANT FOR YOUR PATIENT.

SCHERING CORPORATION • BLOOMFIELD, N. J. EN1486-9

*announcing* A CHANGE IN NAME

SURFAK* FORMERLY DOXICAL

A NEW CHEMICAL

SUPERIOR FECAL SOFTENER

**SURFAK** (formerly Doxical) the new therapeutic chemical, calcium bis-(dioctyl sulfosuccinate) represents a markedly more efficient surfactant softening agent than the older fecal softening chemicals.

■ optimal fecal homogenization ■ greater surfactant effectiveness ■ non-laxative
■ normal physiologic action—no effect on the bowel itself ■ non-habit forming ■ Sodium free

**USUAL ADULT DOSE:** 240 mg. daily. Children and adults (with minimum needs) 50 to 150 mg. daily.
**SUPPLIED:** Surfak 240 mg. capsules—bottles of 15 and 100. Surfak 50 mg. capsules—bottles of 30 and 100.

LLOYD BROTHERS, INC. CINCINNATI 3, OHIO

*Patent Pending

# OFFERS HIGHER BLOOD LEVELS THAN ANY OTHER SALT OF ORAL PENICILLIN:

Now, with Compocillin-VK, patients get blood levels as fast and as high as with intramuscular procaine penicillin. And in most cases, you'll find clinical results are every bit as good as with the injectable. ■ Compocillin-VK may be used whenever oral penicillin therapy is indicated. Dosage range is from 125 mg. (200,000 units) three times daily to 250 mg. (400,000 units) every four hours. Children's dosage is determined by body weight ■ Compocillin-VK Filmtabs 125 mg. (200,000 units), bottles of 50 and 100; 250 mg. (400,000 units), bottles of 25 and 100. Compocillin-VK Granules for Oral Solution come in 40-cc. and 80-cc. bottles. When reconstituted, each 5-cc. teaspoonful represents 125 mg. (200,000 units) of potassium penicillin V.

ABBOTT

# COMPOCILLIN®-VK

*Potassium Penicillin V*

*in tiny, easy-to-swallow Filmtabs* in tasty, cherry-flavored Oral Solution*

*Filmtab—Pat. applied for. U.S. Pat. No. 2,881,085.

906128

# Medicine from Abroad

*FROM POSTGRADUATE MEDICINE'S CORRESPONDENTS*

## AUSTRALIA

***Allergic reactions to penicillin***—In the *Medical Journal of Australia*, N. A. Anderson reported the results of a survey on allergic reactions to penicillin conducted by the Research Committee of the New South Wales Faculty of the Australian College of General Practitioners. The objectives were: (1) to determine the incidence of reactions to penicillin administered orally or by injection; (2) to record the type of reactions and their clinical features; (3) to observe if there is a relationship between the occurrence of reactions and the type of penicillin used (crystalline, procaine or benzathine penicillin, the orally administered forms, and the proprietary preparations).

A reaction developed in 88 (1.3 per cent) of 6,832 patients given penicillin. The proportion of men to women among the allergic patients was 2:1. Six of the seven patients who reacted immediately had received penicillin previously, and three had experienced a reaction. When a benzathine preparation was used, the risk of reaction seemed to increase; there also appeared to be a greater risk of recurrence of symptoms after cessation of treatment with this preparation.

It is important to try to determine whether an anaphylactic reaction is likely to develop in the patient. It may be advisable to make a skin or a conjunctival test. A history of previous reaction or of treatment without reaction is always significant. The possibility of a reaction in patients with an allergic background such as asthma always should be considered.

The series did not reveal any new information regarding the clinical features of allergic responses to penicillin. Reactions were easily classified as immediate or delayed, and the most common features of delayed reactions were urticaria, erythematous rashes, arthralgia and, later, desquamation.

Delayed reactions classically are said to occur after 7 to 10 days of treatment. In this series 24 patients, excluding those who reacted immediately, reacted in the first 24 hours; 33 reacted during the first week, and 14 reacted during the second week. In one patient, classified as having an immediate reaction, urticaria but not anaphylaxis developed. This was a true accelerated reaction of the serum sickness type.

***Roentgenographic examination of the abdomen***—In the same journal, Dr. Patricia Waugh reported that abnormal gas patterns are valuable in diagnosing congenital abnormalities such as atresia of the intestine or imperforation of the anus in children. In the adult, the small intestine does not normally contain gas. However, when an obstruction is present, the gas-distended loops of the intestine arranged in a steplike fashion can be seen, and the fluid levels are visible in the upright view. The fluid includes liquids taken by mouth and secreted digestive juices. In 24 hours, 5 or 6 l. of digestive juices and 2 or 3 l. of fluid taken orally pass through the intestine. The degree of gas distention of the intestine is usually an index of the severity

*(Continued on page A-120)*

# *In Coronary Insufficiency...*

Your high-strung angina patient often expends a "100-yd. dash" worth of cardiac reserve through needless excitement.

## Curbs emotion as it boosts coronary blood supply

**CONTROL OF EMOTIONAL EXERTION** with Miltrate leaves him more freedom for physical activity.

**IMPROVED CORONARY BLOOD SUPPLY** with Miltrate increases his exercise tolerance.

# Miltrate*

Miltown® (*meprobamate*) + PETN

**Each tablet contains:** 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.
**Supplied:** Bottles of 50 tablets.
**Usual dosage:** 1 or 2 tablets q.i.d. *before meals* and at bedtime. Dosage should be individualized.

WALLACE LABORATORIES · *New Brunswick, N. J.*

CML-9159-59 *TRADE-MARK

of the obstruction, and it also indicates that the obstruction is situated in the lower part of the intestine. Fluid levels may be present in three to six hours, but are rarely visible before 10 or 12 hours. If they are not evident within 24 hours. the diagnosis of obstruction is very unlikely.

Obstruction of the large intestine is characterized by distention of the intestine extending to the periphery. Deflation of the intestine distal to the obstruction often indicates the point of obstruction. The small intestine also may be distended and may contain fluid. Peritonitis should be suspected if the loops of the intestine are separated by a distance of more than 3 mm. Adynamic ileus usually involves both the small and the large intestine, and the fluid levels are less evident.

In volvulus of the sigmoid colon, an enormously distended sigmoid loop is visible. A characteristic feature is the converging of three lines to the point of torsion. Volvulus of the cecum also may occur; in this condition, the cecum is greatly distended and displaced upward and to the left.

Elevation of the diaphragm, the presence of gas beneath it, an increased haziness due to fluid beneath or above the diaphragm, and patchy atelectasis of the base of the lung are roentgenographic signs of a subphrenic abscess.

## AUSTRIA

***Paroxysmal tachycardia in the newborn***—At a scientific session of the Pediatric Society of Vienna, H. O. Ruziczka described the case of an infant with cyanosis, edema, hemorrhages of the skin, and enlargement of the liver. The electrocardiogram showed paroxysmal tachycardia, which probably began when the child was 10 or 11 days old. The infant's condition slowly improved with the administration of Myostrophan and CEDILANID®. About six weeks later, the pulse rate again increased, with beats up to 300 per minute; when Cedilanid medication subsequently was reduced, another attack ensued.

Commenting on this case, H. E. Zweymüller asked what changes were seen in the blood sedimentation rate, as this determination seems to be especially significant in ascertaining the cause of paroxysmal tachycardia. The condition is often ascribed to infectious diseases, but in the absence of such disease it possibly could be due to disorder of the central or autonomous regulation of the heart. Another question considered was whether or not the child had been injured during delivery, since intracranial damage also has been thought to cause paroxysmal tachycardia.

Attempted pressure on the carotid sinus, on the eyeball, and on both had no effect in this case, although such pressure has had beneficial effects in older children with paroxysmal tachycardia. Mannheimer and Landtman recommended neostigmine or PROSTIGMIN® to prevent tachycardia. It was suggested that because the prognosis depends on the frequency of recurrent attacks it is worthwhile to try a small maintenance dosage of LARGACTIL®.

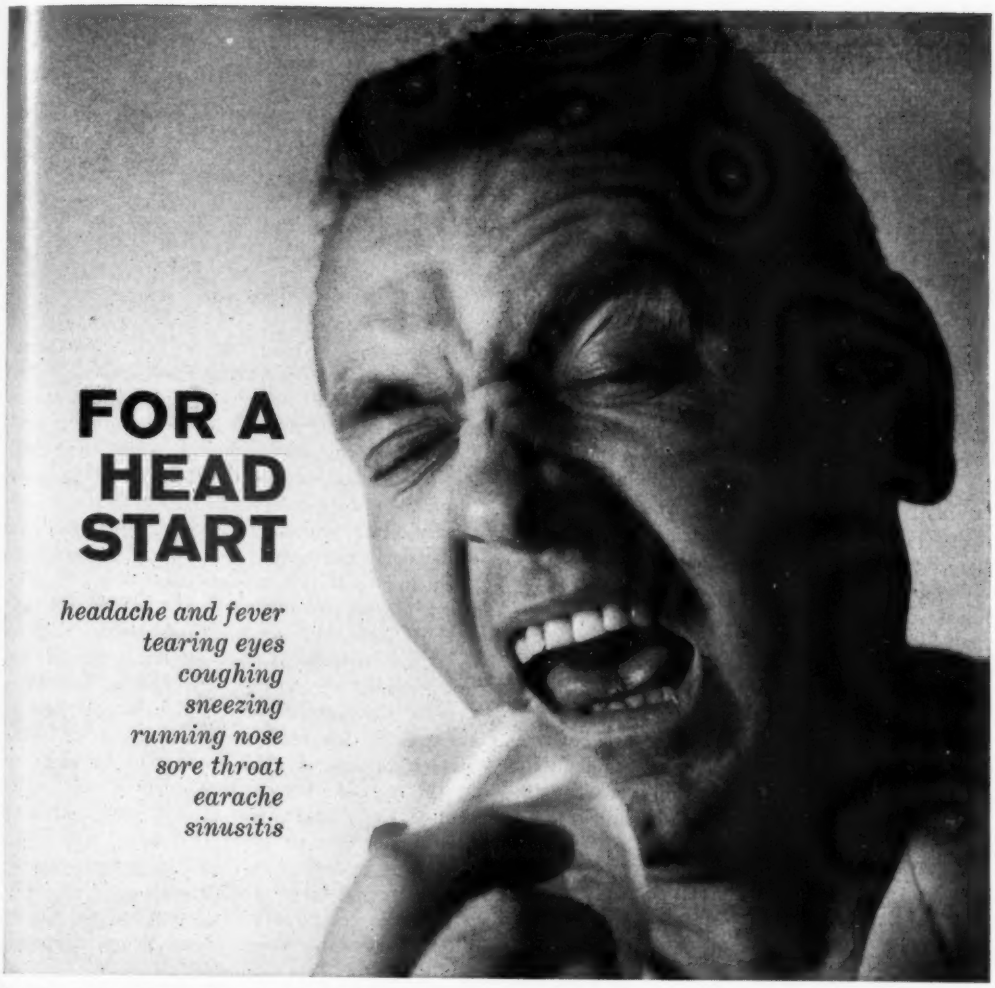
H. W. Swoboda referred to comprehensive statistics which indicate that 50 per cent of all cases of paroxysmal tachycardia start in the first four months of life. Evidently, a majority of patients do not have easily recognizable symptoms, particularly heart-failure. The remedy of choice is digitalis, which nearly always produces good results in this age group.

***Congenital lobar emphysema***—At another meeting of the Pediatric Society of Vienna, H. G. Wolf described a six month old child with congenital lobar emphysema, a disease observed in Austria for the first time. Clinical symptoms are difficulty in breathing and an increased rate of respiration, but the actual diagnosis is based on x-ray findings. Cause of the condition may be a malformation of the bronchial tree, with absence of the bronchial cartilage. The treatment of choice is early lobectomy.

***Mediastinal pleurisy of the anterior right upper segment***—At the same meeting, H. O. Ruziczka described a condition in a five week old infant. The child had fever, catarrhal symptoms, infiltrative changes in the apical segment of the right upper pulmonary lobe, and a typical radiopacity in the right paratracheal area, with projections into the interlobar fissure. These findings, with the clinical course of the disease and an almost complete disappearance of the radiologically observed changes within a week, confirmed the diagnosis of pleurisy in the anterior right upper portion of the mediastinal pleura.

A similar condition in a nine month old child was described by H. E. Zweymüller. The various conditions considered in the differential diagno-

*(Continued on page A-122)*



# FOR A HEAD START

*headache and fever*
*tearing eyes*
*coughing*
*sneezing*
*running nose*
*sore throat*
*earache*
*sinusitis*

## IN UPPER RESPIRATORY INFECTIONS

# COSA-TETRACYDIN*

glucosamine-potentiated tetracycline – analgesic – antihistamine compound

**CAPSULES**

- *Quick, symptomatic relief*
- *Effective in the control and prevention of secondary complications*

Each capsule provides:

| | |
|---|---|
| Cosa-Tetracyn | 125 mg. |
| phenacetin | 120 mg. |
| caffeine | 30 mg. |
| salicylamide | 150 mg. |
| buclizine HCl | 15 mg. |

Additional information on Cosa-Tetracydin is available from the Medical Department of Pfizer Laboratories on request.

Pfizer *Science for the world's well-being™*

**PFIZER LABORATORIES** Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.

*trademark

sis were mediastinal pleurisy of the anterior right upper segment, atelectasis of a segment of the upper lobe, and enlargement of the thymus gland. This case was important because a puncture made in the opaque area yielded no fluid at aspiration and because tomographic studies suggested an occlusion in the area of the bronchus of the right upper lobe. ACTH tests suggested that the opacity was due to an enlarged thymus. It was emphasized that even with careful study the characteristic radiopaque shadow on the x-ray could not be identified with certainty.

H. E. Deutsch considered it likely that in the first case mentioned a pneumonic infiltration with associated pleurisy was actually present in the upper lobe. However, similar x-ray images also would be seen with atelectasis of the upper lobe. In the second case, the right upper field of the chest film was definitely more opaque than was the left. On the tomogram, the site of origin of the upper lobe bronchus, which became lost in this shadow, could be seen. The bronchus of the middle lobe could be clearly recognized as being pulled somewhat upward. This case illustrated that in viewing similar images one must consider the possibility of atelectasis of the entire upper lobe or of one of its segments, a possible enlargement of the thymus, and pleurisy.

H. G. Wolf concluded that on the basis of the demonstrated roentgenograms it was difficult to make a differential diagnosis of the paramediastinal shadows on the right side, which were shaped like a sail. In the absence of a puncture or a postmortem examination, proof of mediastinal pleurisy can be established only by a long series of tests. Diagnosis based on the interpretation of doubtful roentgenographic images is chiefly speculative. Dr. Wolf believes that the frequency of mediastinal pleurisy is overestimated by a few physicians.

H. K. Kundratitz concluded that only differences of opinion were introduced in the discussion of this problem. He emphasized that the roentgenographic shadow of the thymus is capable of producing very unexpected images. In pointing out that the ACTH test and roentgen ray irradiation could bring about temporary changes in the thymus, he mentioned the possibility of toxicosis of the thymus. The thymus also could expand into the interlobar fissure as far as the thoracic wall. Dr. Kundratitz believes that differential diagnosis between an enlarged thymus, atelectasis and pleurisy will always be difficult.

## ENGLAND

***Annual report of the Ministry of Health***—The Ministry of Health has just published its annual report for 1958, from which it appears that the cost of the National Health Service is still rising. The total cost last year was £626 million (approximately $1,878 million), more than £41 million above that of the previous year. The net expenditure on hospital and specialist services was £338,707,000 (approximately $1 billion). One is glad to notice that at last a substantial hospital building and rebuilding program, including more than 100 large projects, is under way. Thirty-six of these projects, costing nearly £30 million (approximately $100 million) had been completed or were nearly completed.

During 1958, pharmacists dispensed 203,384,933 prescriptions at a total cost of £65,475,000 (about $200 million) and an average cost of 6s. 5.26d. (nearly $1.00). The total number of prescriptions was nearly four million less than that for the previous year, which was the lowest since 1949. The total cost was over £4,500,000 more than that of 1957 because of an increase in the average prescription cost of 6.5d. (10 cents). The increase was largely attributable to the higher cost of drugs supplied, which, in turn, was caused chiefly by the prescribing of the newer and more expensive drugs.

In 1958, proprietary drugs represented nearly three-quarters by value of all drugs supplied, and the ingredients alone cost about £29 million. The initial application of a scheme for the voluntary regulation by pharmaceutical manufacturers of the prices of certain proprietary preparations had resulted in price reductions equivalent to about £400,000 (about $1,200,000) a year.

***Sensitivity to poliomyelitis vaccine***—Untoward reactions to poliomyelitis vaccination are uncommon, and it is generally agreed that poliomyelitis vaccine is exceedingly safe to use. Although the vaccine has been administered many thousands of times in both England and the United States, reports of unpleasant sequelae have been few. Nevertheless, from the reports that are available, it is clear that allergic reactions may occur. Usually, the skin is involved.

*(Continued on page A-124)*

Raudixin–the cornerstone of antihypertensive therapy–helps relieve the pressures in your patients–helps relieve the pressures on your patients / 50 and 100 mg. tablets whole root rauwolfia for exceptional patient response

SQUIBB Squibb Quality—the Priceless Ingredient

Squibb Whole Root Rauwolfia Serpentina/'RAUDIXIN'® IS A SQUIBB TRADEMARK

but general systemic upsets also have been described. In most cases, traces of penicillin in the vaccine have been suspected of being the sensitizing agent.

Drs. W. O. Thomson and Duncan Fletcher, Department of Health and Welfare, Glasgow, have recently published in the *British Medical Journal* an interesting case report of a nurse who was sensitive to penicillin and, to a lesser degree, to streptomycin. Angioneurotic edema and mild shock developed in this patient after the injection of 1 ml. of poliomyelitis vaccine; 41 days later, a similar reaction followed the intradermal injection of 0.1 ml. of the vaccine.

In the preparation of poliomyelitis vaccine not more than 200 units each of penicillin and streptomycin is present in the original culture medium; much smaller concentrations are used in the final product. In spite of the fact that the quantities are exceedingly small, they still would seem capable of producing anaphylactic reactions in sensitive subjects. While the other components of poliomyelitis vaccine cannot be eliminated, it would seem, from the patient's past history of sensitivity to penicillin and streptomycin, that one or both of these antibiotics were responsible for the reaction. This would mean that she reacted to something in the nature of 2 units of penicillin or less than 20 units of streptomycin, or both, given intradermally.

The authors advise that before poliomyelitis vaccine is administered it is essential that the patient (or, if the patient is a child, the parent) should be asked if there is a history of sensitivity to penicillin or streptomycin. If there is any doubt, a test dose should be given intradermally. Particular attention should be paid to those who frequently work with these antibiotics. For those who are penicillin-sensitive, a penicillin-free vaccine should be available similar to that obtainable in the United States. If it is available, penicillinase should be given before the vaccination. The principal safeguard, however, is to make certain that the physician is aware of the potential risk to patients sensitive to penicillin or streptomycin.

## FINLAND

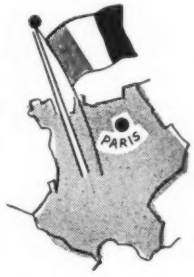
***Mortality due to cardiovascular diseases in Helsinki***—According to a report by E. Varpela in *Duodecim*, no abrupt changes occurred between 1915 and 1954 in the total mortality from cardiovascular diseases in residents of Helsinki between 30 and 69 years of age. However, mortality from these diseases decreased in younger persons and increased in the older age groups. There are indications that changes also occurred in the qualitative composition of cardiovascular diseases. This might be expected, since these diseases differ in pathogenesis. Thus, it is possible that the age-standardized mortality from coronary disease has increased.

Although fewer deaths due to coronary disease were recorded in Helsinki during World War II, especially among women, an increased number of deaths caused by myocardial disease in both men and women and by hypertension and cerebral apoplexy in women resulted in an increase in the total mortality from cardiovascular diseases. This was especially noticeable in the female population.

Further study showed that environment did not affect the mortality from cardiovascular disease in the various groups mentioned. Thus, it was suggested that these diseases are partly of a hereditary nature. Persons coming to Helsinki from old agricultural regions have the highest mortality from cardiovascular diseases. This may be due to the fact that these people have some difficulty in adapting to the factors of civilization which influence the pathogenesis of cardiovascular diseases.

This survey also showed that different types of cardiovascular disease developed within various groups of the population. This may be because of the variance in each group's contact with the different pathogenic factors in these diseases. Comparison of the mortality from coronary disease and that from cerebral apoplexy was particularly interesting.

## FRANCE




***Lichen planus from solutions used in color photography***—Eight cases of lichen planus in patients whose occupation was developing color photographs were described by Dr. Pierre de Gracianski et al. in *La Presse médicale*.

The workers were affected a few weeks after they had been assigned to their jobs. In some

*(Continued on page A-126)*

# Knock the stuffings" out of head-cold stuffiness

**Sniffles and stuffiness "take the count" —'round-the-clock—with**

# Naldecon™

The long-acting nasal decongestant with the therapeutic "one-two" tablets

Awake or asleep, your "cold patient" can be kept comfortably free of nasal dripping and congestion, watery eyes and stuffy head. These distressing symptoms are gently but effectively "knocked out" by long-acting Naldecon's therapeutic one-two:

**"One"**—a combination of 2 potent decongestants, to reduce mucosal swelling.

**"Two"**—a combination of 2 dependable antihistaminics, to relieve allergic symptoms.

Relief — within minutes — is easily maintained 'round-the-clock, with t.i.d. dosage of this unique nasal decongestant.

**BRISTOL LABORATORIES INC.**
**SYRACUSE, NEW YORK**

**NALDECON TABLETS**

Each long-acting NALDECON "tablet-within-a-tablet" contains:

| | Outer Layer (3 to 4 hours relief) | Inner Core (additional 3 to 4 hours relief) | Total Content (6 to 8 hours relief) |
|---|---|---|---|
| DECONGESTANTS: | | | |
| Phenylephrine HCl | 5 mg. | 5 mg. | 10 mg. |
| Phenylpropanolamine HCl | 20 mg. | 20 mg. | 40 mg. |
| ANTIHISTAMINICS: | | | |
| Phenyltoloxamine citrate | 7.5 mg. | 7.5 mg. | 15 mg. |
| Chlorpheniramine maleate | 2.5 mg. | 2.5 mg. | 5 mg. |

**Dosage, Naldecon Tablets** — Adults and children over 12: One tablet morning, afternoon and evening for 'round-the-clock relief. Children 6 to 12: One-half tablet morning, afternoon and evening.

**Also available — NALDECON SYRUP**

Each teaspoonful (5 cc.) of NALDECON Syrup contains: phenylephrine HCl, 5 mg.; phenylpropanolamine HCl, 20 mg.; phenyltoloxamine citrate, 7.5 mg., and chlorpheniramine maleate, 2.5 mg.

**Dosage, Naldecon Syrup**—Adults and children over 12: One tsp. (5 cc.) every 3 or 4 hours. Children 6 to 12: One-half tsp. every 3 or 4 hours. Under 6: In proportion.

patients it began as an unmixed exanthem; in others, it was superimposed on eruptions which resembled the ordinary edematous vesicular types of contact dermatitis. Cyanotic polygonal papules were formed. When the patient discontinued his work, the eczematoid dermatitis cleared, but the lichen planus remained for several weeks.

Clinically, this lichen eruption was not remarkable; it consisted of papules, oozing stripes, a mucosal condition in the fern-leaf shape, and pigmented sequelae. The histologic picture was typical: hyperkeratosis, hypergranulosis, hyperacanthosis, and destruction of the basal membrane by a band-shaped lymphocytic infiltration with an almost straight-line aspect at the boundary of the epidermis and subcutis. Atrophic zones could be seen in the basal membrane and the mucosal body; however, the initial lesions were eczematoid.

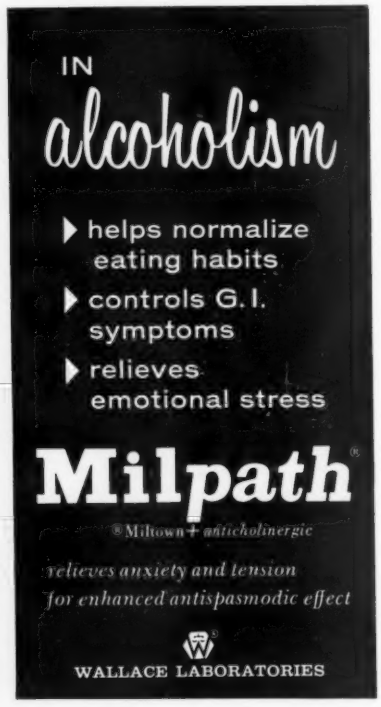
The chemicals used in developing color photographs are derivatives of paraphenylenediamine, a compound well known to cause eczema. The three substances in question were a chlorhydrate and two sulfates, all in 3 per cent alkaline solutions. Their causative role was shown by these facts: (1) None of these workers had been previously affected by a skin disease; (2) the eruptions occurred in patients whose work exposed them to contact with color developers, especially in preparing solutions, developing photographs, or repairing tanks containing the compounds; (3) cure was achieved soon after leaving this work if the eruption was recent, but slowly if the rash was chronic; (4) sooner or later, almost all employees were affected and could work at these jobs only for short periods, with the intervals spent in other work; (5) the initial lesions appeared on the hands and forearms; and (6) skin tests were positive.

The skin tests were positive with two of the three compounds which the workers handled; they were negative with the third compound whose amine radical was blocked by a sulfonamide chain and with the carbon which reduced the compound's sensitizing power. In the control subjects, all the tests gave negative results. In the affected persons, the control tests remained negative with compounds of related chemical formulas and with sulfonamides, PHENERGAN® and other paraphenylenediamines. The clinical aspect of the tests was identical to that usually obtained with the various skin sensitizers. The test reaction was edematous vesicular and not lichenoid in appearance.

These observations are entirely different from those of contact dermatitis. Lichen planus produced by contact sensitization had never been observed or reported. Lichen planus is recognized as a toxic dermatitis of internal origin, due particularly to arsenic, bismuth, mercury and gold. Recently, it has also been observed after the absorption of mepacrine. It either arises in the course of an ordinary erythroderma, or appears as lichen from the start, as in the patients studied. Eruptions of lichen can be triggered by local causes, by irritation from friction, or by radiotherapy, but they do not appear to result from sensitizing contact.

The author suggests that in these patients, the lichen was due not to contact of the skin with the color-producing substances but to inhalation of the powder of the compounds while preparing the solutions. It would thus be a dermatosis of internal origin.

The question of compensation of the affected workers has also arisen. French law only allows compensation for certain plainly qualified dermatoses, but the classification of "dermatoses provoked by aromatic amines" is a vague one, and without further difficulties these cases of lichen planus can hardly be included in this class.



# Strokes as a Neurosurgeon Sees Them

E. HARRY BOTTERELL*

*University of Toronto Faculty of Medicine, Toronto*

*Various pathologic processes amenable to treatment masquerade as strokes; subdural hematoma can mimic almost any neurologic syndrome.*

*There is almost universal agreement that the origin of subarachnoid hemorrhage or the artery involved in strokes cannot be located without arteriography.*

*Intracranial aneurysms tend to form intercerebral clots if they bleed. A patient with subarachnoid hemorrhage should be transferred to a neurosurgical unit able to deal with arteriovenous malformations and aneurysms.*

*When there is thrombosis in one internal carotid artery, other arteries commonly are involved also. Results of surgical treatment are fairly good in selected cases.*

E. HARRY BOTTERELL

WHAT is a stroke? The Oxford dictionary defines it in a variety of ways: an act of striking; a blow given or received; a blow with the hand or a weapon, occasionally with the paw of an animal, inflicted on or by a human being; an act which causes pain, injury or death; often an act of divine chastisement or vengeance; a calamitous event; a damaging or destructive discharge, lightning, and so on. About midway among the various definitions a stroke is described as an attack of disease, an apoplectic or paralytic seizure. That is a pretty broad definition, and, indeed, I do not believe there is any such thing in medical diagnosis accurately phrased as a stroke.

It is not seemly for a neurologic surgeon to venture into the fields of malignant hypertension, periarteritis nodosa, subacute bacterial endocarditis, and the like. Rather, I propose to call again to your attention some of the common pathologic lesions which bring patients to general hospitals with the diagnosis of a stroke. Once upon a time when I was a medical student, all pathologic processes were approached diagnostically under the headings of inflammation, trauma, tumor, tuberculosis

*Associate Professor of Surgery (Neurosurgery), University of Toronto Faculty of Medicine, Toronto, Ontario, Canada.

Presented before the forty-third annual Assembly of the Interstate Postgraduate Medical Association at Cleveland.



UNIVERSITY OF MICHIGAN LIBRARIES

and syphilis. I do not propose to work out a classification of strokes with you, but rather I seek to persuade you to have an even more open mind.

I would emphasize to you that the circle of Willis is fed by two vertebral arteries and two internal carotid arteries, and I would hope that from this moment on you would think of the "carotid-vertebral" blood supply to the brain, not the carotid *or* the vertebral. I would have you think of the circle of Willis as a gas ring, as Symonds once said, or, perhaps, in this day and age, as a series of oil pipelines electronically regulated by feedback mechanisms so that if one vertebral or carotid artery is shut off the others take over, given time. This is a basic concept which I think I can document briefly here.

### *Intracranial Hemorrhage at Various Ages*

Little need be said to this audience concerning cerebrovascular hemorrhage in aged persons, whether they are aged chronologically or pathologically, but the subject of intracranial hemorrhage does open up a new field of "strokes" occurring in middle-aged and elderly persons and occasionally in persons in their twenties and younger.

A sudden paroxysmal headache with a stiff neck and meningeal irritation is indicative of subarachnoid hemorrhage. A representative case is that of a woman who had a terrible headache and a third nerve paralysis. One eye was closed. One could almost make the diagnosis from this evidence. She had an aneurysm of the internal carotid artery at the level of the posterior communicating artery. The headache is caused by meningeal irritation from blood in the subarachnoid space. Pressure on the third nerve is a local effect of the aneurysm. The aneurysm was clipped, and the patient is alive and well 10 years later.

I want to present a patient who kindly consented to come here today. She is a lady from Cleveland who had a subarachnoid hemorrhage and a terrible headache as she was getting dressed for church. She was unconscious for 15 minutes and was taken to the Cleveland City Hospital, where a cervical carotid ligation was done for a ruptured carotid aneurysm. She has no sequelae whatsoever, and is working as a practical nurse. She has no weakness or disturbance of vision, and she talks normally, giving a clear history. The lesion was on the left side and she is right-handed. Her history is typical. She did not have a third nerve paralysis. She has lost one carotid artery; it is completely shut off, so the other carotid artery and the vertebral arteries are nourishing her brain effectively.

These aneurysms have a great tendency to form intercerebral clots if they bleed, thus producing space-occupying lesions. The evacuation of such a clot may save the patient's life, as it did in the case of a 40 year old patient who had a ruptured aneurysm of the middle cerebral artery—a "stroke," if you like, in middle age. A temporal lobe clot was evacuated, the aneurysm was disposed of, and the patient is alive and well.

Recently a story appeared in the papers about a girl of 12 years who died suddenly on the way to school. She had not had heart trouble and had been considered perfectly well. She had an arteriovenous malformation in her brain which bled into the brain and subarachnoid space—a "stroke" in childhood, and a fatal one!

Aneurysms are uncommon in childhood, rare in the teens, and more common with increasing age. Arteriovenous malformations, on the other hand, are common in childhood, not uncommon in middle age, and rare in old age. I think the reason they are rare in old age is that most persons who have arteriovenous malformations die before then. Clearly these thin-walled vessels with blood rushing through them, directly shunting from artery to vein, are very vulnerable to rupture and subarachnoid hemorrhage, and also to intracerebral bleeding.

In a series of 19 cases of arteriovenous malformations in which operation was performed, there were eight instances of intercerebral clot and seven of subarachnoid hemorrhage. There were many other patients who had epilepsy, the third and cardinal sign of an arteriovenous malformation, but many of them were not operated on because of the site of the lesion.

### *Ischemic Infarction*

On the basis of some textbook illustrations of cerebral arterial distribution, one would think that if one cerebral artery is occluded, softening should occur all along that distribution if cerebral arteries are "end arteries." Such is not the case. Ischemic infarction following destruction of the middle cerebral artery is extremely variable, and the same holds for the anterior and posterior cerebral arteries. Certainly there is the circle of Willis, a series of pipelines controlled by feedback mechanisms. It has long been shown that there is a subpial anastomosis between all these arteries.

Cerebral angiography, first done by Moniz, represents the great advance in the study of the circulation of the brain. Let us consider a case in which an angiogram shows the right internal carotid artery and no right anterior cerebral artery. The left carotid angiogram shows filling of both anterior cerebral arteries from the left cerebral stem. It would be most unfortunate, would it not, to clip that particular left anterior cerebral artery or for it to be obstructed by thrombosis based on atheromatous plaques. Massive cerebral infarction probably would result. Or consider a case in which angiograms show a left posterior cerebral artery but none on the right; on the right there is a large posterior communicating artery arising from the internal carotid, coming back and feeding the posterior cerebral distribution. There is such great variation in the circle of Willis that it is difficult to predict what will happen when a particular artery is occluded.

It was Miller Fisher who went down into the neck to look for atheromatous obstruction of the internal carotid arteries. German workers many years ago called attention to thrombosis of the internal carotid arteries in the neck, but it was forgotten. You will recall that in the face of infarction of the brain very often the pathologist could not show a plug in a cerebral artery.

A man who had an occlusion of the internal carotid artery in the neck was admitted to the hospital after having had two or three small strokes during the preceding weeks; he had had perhaps a numb arm and leg for 10 or 15 minutes. While he was being admitted to the hospital, hemiplegia developed suddenly. A carotid arteriogram disclosed occlusion of the internal carotid artery at its origin in the neck. We operated, and fortunately there was a back flow down the internal carotid artery and we were able to restore the circulation. The paralysis involved the side opposite the obstructed artery, but the obstruction was weeks if not months old. His collateral circulation, adequate for some time, had failed; the pipelines did not quite redistribute the flow fast enough.

Another man who had had multiple small strokes, with numbness and weakness of one side of the body for a few minutes, was found to have a partial obstruction of the internal carotid artery in the neck. The small strokes were brought on by anything that reduced the blood pressure and cardiac output. My colleague, Dr. William Lougheed, repaired the artery by a graft.

Hutchison and Yates in Manchester, England, have reported some very important findings in regard to obstruction of the internal carotid arteries. They found stenosis and thrombosis at the origin of the internal carotid arteries and also in the vertebral arteries where they originate at the subclavian. When there is thrombosis in one carotid artery, it is very common for the other arteries to be involved also. In one case reported by Hutchison and Yates, both carotid arteries were totally obstructed and the vertebrals alone carried blood to the brain; nevertheless, the patient got along pretty well.

Some 20 patients with internal carotid obstruction have now been operated on in the Neurosurgical Unit of the Toronto General Hospital. Results are fairly good in selected cases in which the patients have not had massive cerebral infarction. Results have not been at all rewarding in cases in which there is no retrograde flow from the brain downward toward the obstruction, thrombosis has gone solidly up the artery, and hemiplegia has followed cerebral softening due to ischemia. This is in line with Robb's results in London and those of other observers in the United States; if there is an incomplete obstruction with ret-



UNIVERSITY OF MICHIGAN LIBRARIES

rograde flow and little strokes and if massive infarction has not occurred, the results are good. It seems to me that it is logical, where it is possible, to restore the arterial circulation, because if one carotid artery is obstructed it is likely that atheromatous changes have affected the other carotid artery and the vertebral arteries. I do not wish to engage in a controversy about the use of anticoagulants versus surgical relief of arterial obstruction, but it does seem logical to restore the flow in the artery, if you can.

### *Subdural Hematoma, the Great Imitator*

Once upon a time when I was a medical student, to repeat myself, I was led to believe that syphilis was the great imitator. As a neurosurgeon I don't think much of syphilis as an imitator any more, but I do regard subdural hematoma as a great imitator. At one time on our ward we had seven cases of chronic subdural hematoma, and two of the junior house surgeons wrote them up for the students' journal. One case mimicked a basilar artery thrombosis. There was a fairly sudden attack, with spastic paralysis of the leg in extreme form. The patient had not been very well for a bit, and his physician, a most skilled neurologist, said he didn't care if this patient had had a minor injury two months before, causing a chronic subdural hematoma, for he certainly must have basilar artery thrombosis. The subdural hematoma was taken out, and the patient's spastic paralysis disappeared in the next few days.

Subdural hematoma may imitate cerebellar tumors, with unsteadiness of gait the outstanding symptom, or there may be mental deterioration of an atypical type, or papilledema with nothing else but intermittent blurred vision, or pseudobulbar paralysis—almost any neurologic syndrome. Why do I include subdural hematoma in a discussion about strokes? Recently a patient was sent in unconscious. He had had a few fits and had become hemiplegic. Because he was in the older age group, his condition was labeled a stroke. The patient's wife remembered that he had fallen in the bathtub a couple of months before and hit his head. We said we must explore, and he had a chronic subdural hematoma.

If one intelligent observer suspects that a patient may have a subdural hematoma, we insist on exploration. On the occasions when we have failed in this policy we have been dreadfully sorry. An example is the case of a patient sent to us from an outlying community whose referring physicians thought he had a subdural hematoma; several of us, in our wisdom, thought this was impossible, and at autopsy there was a large clot.

How do you diagnose subdural hematoma? By unremitting consciousness of its existence. An x-ray of the skull which shows calcification of the pineal gland and shifting well across the midline is a very useful indication of a space-occupying lesion, be it subdural clot, cerebral swelling, or tumor. There are certain additional aids. A carotid angiogram is very useful. Arteriography has done much to clarify strokes. I venture to say that almost all neurologists and neurosurgeons agree that one cannot localize the origin of subarachnoid hemorrhage or locate regularly the artery involved in small strokes or major strokes without arteriography, because of the collateral circulation and the variability of the circle of Willis.

A patient may be sent in with the diagnosis of a "slow" stroke—gradually increasing paralysis over a period of a few days, and then unconsciousness. An x-ray of the head demonstrates a pineal shift, perhaps, or the patient has papilledema and the slow stroke is a malignant tumor. One has to think about this, because the tumors are not always malignant; they may be subdural hematomas.

The elderly or middle-aged patient who has a discharging ear and a few seizures and who doesn't awake from one of the seizures and is unconscious with a hemiplegia and rapidly becomes more unconscious may have a brain abscess. We have had a number of these cases.

### *Comments on Management*

I should like to take you back on this brief journey through strokes and start off again with the emphasis on the necessity for an open mind about strokes. Let us take intracranial

hemorrhage. We believe that the proper way to treat a patient with subarachnoid hemorrhage, unless he is moribund (and many of them die at once), is to transfer him as soon as it is reasonably possible to do so to a neurosurgical unit fully equipped to deal with arteriovenous malformations and aneurysms.

Angiography will not show all aneurysms. After the arteriogram has been made at the earliest reasonable time, the neurologic surgeon is then in a position to decide whether that particular aneurysm and that particular patient are appropriate for early operation, deferred operation or no operation. We have conducted a most intensive campaign in an attempt to use hypothermic anesthesia to make practicable early operations for ruptured aneurysms and avoid these recurrent hemorrhages that cause death. We have been only partly successful, and whether or not, in our view, a patient should be operated on early depends on his age, the degree of atherosclerosis, how much collateral circulation exists, the size and site of the aneurysm, and how much the brain has been injured by the hemorrhage. Subarachnoid hemorrhage from rupture of an aneurysm is the wrong term; these aneurysms commonly rupture into the brain, and very often there is ischemic softening which may accompany the rupture or follow it, because the artery responds to hemorrhage by spasm.

Therefore, early transfer of patients with subarachnoid hemorrhage or ruptured aneurysm is important; the patient is no worse off lying on a stretcher in an ambulance than in his own bed. The unconscious patient should always be transported in a semiprone position.

In this day and age of small strokes I think it requires decision about angiography by neurologist or neurologic surgeon, or both, before one can quietly say that somebody who is having recurring attacks of weakness or numbness or difficulty talking can be written off. The decision must be made whether to use anticoagulants, to try and restore the circulation by thrombendarterectomy or grafting, or to combine both measures.

Finally, subdural hematomas are where you find them. I am reminded of a story by the late Campbell Howard, who was one of my chiefs and taught me more than I can ever admit. He visited Iowa to see if he would go there as professor of medicine. Subacute combined sclerosis was his special interest at the time, and in answer to his inquiry about it he was told, "There is no subacute combined sclerosis in Iowa; we don't have it." He told me with great enthusiasm years later when he returned to McGill that in the first five years in Iowa he found a goodly number of cases of subacute combined sclerosis. So it is with subdural hematoma. If you are aware of it and think about it in every neurologic case, you will make most rewarding diagnoses.



UNIVERSITY OF MICHIGAN LIBRARIES

# The Practical Aspects of Anemia Therapy in Pregnancy

ROY G. HOLLY*

*University of Nebraska College of Medicine, Omaha*

*Either oral or intramuscular iron may be administered in the therapy of iron-deficiency states associated with pregnancy. Response to oral iron salts is adequate but gradual and slow. If sufficient time is available prior to delivery, oral therapy is preferred. Intramuscular injection of iron is a safe method with relatively few side effects, and the hematologic response often is dramatic.*

ROY G. HOLLY

A SIMPLE classification of the anemias associated with pregnancy divides them into two main categories: (1) certain anemias coexisting with but not related to the pregnancy, e.g., familial hemolytic and sickle cell anemias, and (2) anemias more directly related to the pregnant state and occurring because the woman is pregnant. Examples of this group include iron-deficiency, hypoplastic and megaloblastic anemias.

Megaloblastic and hypoplastic anemias are interesting but rare entities. Megaloblastic anemia usually occurs with a nutritional deficiency and is characterized by the megaloblastic change in the bone marrow. It is most adequately treated by means of folic acid. Hypoplastic anemia is a refractory anemia and occurs secondary to bone marrow repression. With the exception of cobaltous chloride, presently known hematinics have not proved to be effective in its treatment. Transfusions with whole blood may be necessary to maintain normal hematologic values.

Because iron-deficiency anemia is the predominant type, this discussion will emphasize the practical aspects of iron therapy. First, however, I will review certain features of iron metabolism, since the prevention and therapy of deficiency states demand a working knowledge of iron metabolism.

*Chairman and Professor, Department of Obstetrics and Gynecology, University of Nebraska College of Medicine, Omaha, Nebraska.

Presented before the forty-third annual Assembly of the Interstate Postgraduate Medical Association at Cleveland.

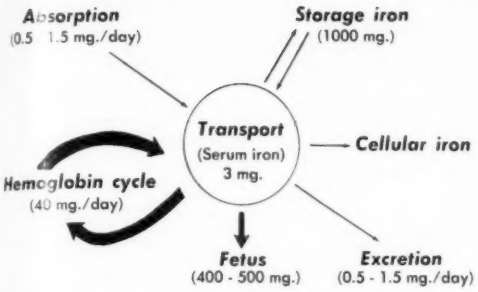



FIGURE 1. Iron metabolism in pregnancy.

### *Iron Metabolism in Pregnancy*

The schematic drawing in figure 1 depicts iron metabolism during pregnancy. The total body iron in the female amounts to 3.5 to 4 gm., of which 70 to 75 per cent is contained in the hemoglobin molecule. Another 15 to 20 per cent is storage iron. One of the more significant features of iron metabolism is that only small quantities are absorbed and excreted each day. The body actually conserves iron by not excreting it, and attempts to control body iron by rigidly limiting the amount which is absorbed. The amount of iron in our diets may vary from 7 to 12 mg. a day. Less than 10 per cent of this is absorbed, so we may assume that 0.5 to 1.5 mg. of the ingested iron crosses the intestinal cell barrier and reaches the body's iron pool. A similar small quantity is excreted.

More iron may be absorbed under conditions of iron need, but probably not more than 4 or 5 mg. for any 24 hour period. This restricted absorption of elemental iron definitely limits the speed with which hemoglobin repair may proceed when iron is administered orally. It should be stressed that only the ferrous form of iron is absorbed.

Iron is stored in the liver, spleen and bone marrow. The 1000 to 1500 mg. of iron normally held in reserve is "available iron," for it is readily withdrawn for use elsewhere in the body if the demand arises. Because of pregnancy and menstruation, most women have partially or completely depleted iron stores at all times. So far as I can determine, the amount of storage iron is the most important single factor determining a woman's hematologic status during pregnancy. Figure 2 depicts the relationship of hemoglobin to storage iron. As long as there is "available" or storage iron, the hemoglobin concentration remains within normal limits. Anemia from iron deficiency occurs only when the iron reserves are completely depleted. The converse is true, for as iron is given to the iron-deficient subject all of it is used for hemoglobin synthesis; it is not stored until these demands are satisfied.

As indicated previously, most women during their reproductive years have less than normal iron reserves. We assume that most women enter pregnancy with insufficient reserves to meet the iron demands pregnancy creates. Recently published investigations on storage iron in pregnancy revealed that only one of 12 patients had normal reserves at the

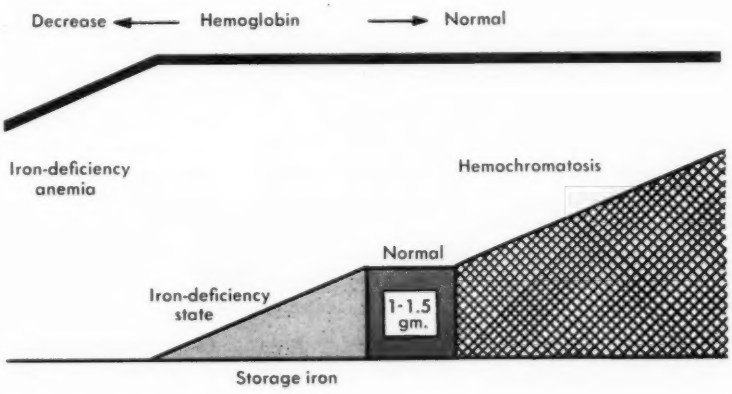



FIGURE 2. Relation of hemoglobin to storage iron. As long as there is available iron, hemoglobin concentration remains within normal limits. Anemia from iron deficiency occurs only when iron reserves are depleted.

TABLE 1

STORAGE IRON IN EARLY PREGNANCY

| PATIENT | AGE | PARITY | HEMOGLOBIN (GRAMS PER 100 ML.) | HEMATOCRIT (PER CENT) | STORAGE IRON |
|---|---|---|---|---|---|
| N. S. | 24 | 4 | 11.4 | 36 | 3+* |
| B. T. | 22 | 1 | 13.1 | 40 | 1+ |
| M. H. | 41 | 3 | 13.1 | 41 | 1+ |
| P. M. | 20 | 2 | 12.5 | 39 | 1+ |
| S. C. | 20 | 4 | 12.4 | 42 | Trace |
| E. K. | 17 | 0 | 11.7 | 39 | Trace |
| A. W. | 29 | 6 | 11.4 | 39 | 0 |
| G. M. | 24 | 5 | 10.8 | 36 | 0 |
| C. H. | 18 | 0 | 10.1 | 33 | 0 |
| R. S. | 29 | 3 | 9.6 | 30 | 0 |
| M. W. | 28 | 7 | 9.3 | 31 | 0 |
| A. Y. | 26 | 4 | 9.1 | 33 | 0 |

*Intramuscular iron given during previous pregnancy.

outset of gestation, and it is significant that she had received a generous quantity of iron intramuscularly about a year earlier (table 1). The iron-storage estimates were made by staining bone marrow particles with potassium ferrocyanide.

A hypothetical situation such as the one in figure 3 serves to illustrate the shifts of iron in pregnancy. Certain assumptions have been made, namely, that the initial hemoglobin level was 13 gm., the total blood volume was 4000 ml., and 300 mg. of iron was contained in reserve; further, during the pregnancy the blood volume rose to 5000 ml., and iron absorption exceeded excretion by 0.5 mg. per day. The bar graphs on the left show the distribution of iron early in pregnancy. A hemoglobin mass of 520 gm. contains about 1800 mg. of iron. During pregnancy the fetus removes from the maternal iron pool an amount roughly equivalent to that absorbed and that held in reserve. Consequently the hemoglobin mass cannot increase, and within a total blood volume of 5000 ml. the hemoglobin concentration falls to 10.4 gm. Actual study has confirmed the essential facts behind the hypothetical situation. With more iron in reserve or with iron supplementation, the iron for the extra hemoglobin synthesis would have been available and the hemoglobin concentration would not have decreased.

Table 2 shows serial storage iron estimates in five patients during pregnancy. In each instance where storage iron was demonstrated early in pregnancy, less was demonstrated late in the gestation. Those patients with minimal

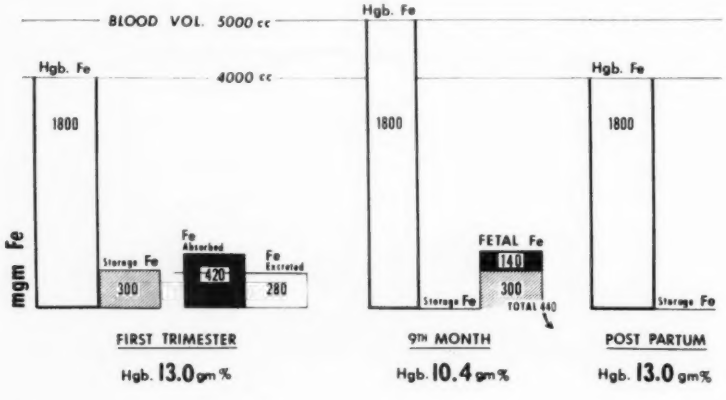



FIGURE 3. The shifts of iron in pregnancy. During pregnancy the fetus removes from the maternal iron pool an amount roughly equivalent to that absorbed and that held in reserve. Consequently the hemoglobin mass cannot increase, and the concentration falls.

TABLE 2

COMPARISON OF STORAGE IRON IN EARLY AND LATE PREGNANCY WITHOUT IRON THERAPY

| PATIENT | DIAGNOSIS | TIME INTERVAL (DAYS) | AGE | PARITY | HEMOGLOBIN (GRAMS PER 100 ML.) | SERUM IRON (GAMMA PER CENT) | STORAGE IRON |
|---|---|---|---|---|---|---|---|
| S. C. | Early pregnancy | | 20 | 4 | 12.4 | 93 | Trace |
| | Late pregnancy | 174 | | | 10.8 | 36 | 0 |
| B. T. | Early pregnancy | | 22 | 1 | 13.1 | 119 | 1+ |
| | Late pregnancy | 165 | | | 12.8 | 89 | Trace |
| M. H. | Early pregnancy | | 41 | 3 | 13.1 | 97 | 1+ |
| | Late pregnancy | 158 | | | 13.4 | 64 | Trace |
| E. K. | Early pregnancy | | 17 | 0 | 11.7 | 106 | Trace |
| | Late pregnancy | 149 | | | 11.2 | | 0 |
| N. S. | Early pregnancy | | 24 | 4 | 11.4 | 84 | 3+* |
| | Late pregnancy | 84 | | | 11.1 | 72 | 1+ |

*Intramuscular iron given during previous pregnancy.

depletion of iron reserves (1+ reaction) were able to proceed through pregnancy without a significant decrease in hematologic values. We know that iron is essential for a normal hemoglobin concentration. The demands for iron during pregnancy are increased to supply the fetus and to synthesize a larger hemoglobin mass. This iron must come from the storage depots or from exogenous sources.

Investigations utilizing radioactive iron have shown that approximately 30 to 40 mg. of iron is required to synthesize new hemoglobin each day to replace that normally degraded. This is the normal hemoglobin repair and breakdown cycle. The iron liberated in the process of red cell degradation is returned for use in the synthesis of new hemoglobin. My studies with iron-deficient subjects have shown that this amount of iron involved decreases to 10 to 15 mg. per day. If oral iron is administered and only a small quantity is absorbed, it is obvious that the supply of iron available for new hemoglobin synthesis is less than optimal. The hemoglobin repair is at best gradual and slow.

### *Principles of Iron Therapy*

The basic principles involved in iron therapy are as follows: (1) Eliminate the source of iron loss if possible. (2) Calculate the iron requirement. (3) Select the route of administration and provide via that method the required amount of iron. Iron therapy is too often insufficient, with small doses administered for too short a time. Calculation of the total iron requirement serves as the basis for administering the proper amounts of iron. It should be stressed that iron therapy should provide iron for hemoglobin repair and in addition provide iron for storage.

### *Calculation of the Iron Requirement*

The formula for calculating the iron requirement is as follows:

$$\left[\frac{13.5 - Y}{100} \times \text{blood volume} \times 3.4\right] + 500 = \text{Fe mg.}$$

A normal hemoglobin of 13.5 gm. is assumed for the female. Y is the patient's hemoglobin. The blood volume can be estimated as 65 ml. per kilogram of body water. The value 3.4 converts grams of hemoglobin to milligrams of iron. The portion of the formula within the brackets provides the quantity of iron necessary to raise the hemoglobin from Y to 13.5 gm. To this amount 500 mg. of the element is added to provide iron for storage.

TABLE 3

COMPARISON OF HEMOGLOBIN CONCENTRATION AT THE THIRD TO THE SIXTH MONTH OF PREGNANCY WITH THE PREDELIVERY VALUE

| SERIES | TOTAL NUMBER OF PATIENTS | HEMOGLOBIN (GRAMS PER 100 ML.) | | | | |
|---|---|---|---|---|---|---|
| | | *9.0-9.9* | *10.0-10.9* | *11.0-11.9* | *12.0-12.9* | *13+* |
| Untreated | 55 | | | | | |
| 3 to 6 Mo. | | 0 | 5 | 15 | 20 | 15 |
| Predelivery | | 6 | 17 | 13 | 13 | 6 |
| Iron-treated | 94 | | | | | |
| 3 to 6 Mo. | | 0 | 9 | 26 | 38 | 21 |
| Predelivery | | 0 | 1 | 15 | 32 | 46 |
| Iron-cobalt | 58 | | | | | |
| 3 to 6 Mo. | | 0 | 5 | 18 | 22 | 13 |
| Predelivery | | 0 | 1 | 5 | 15 | 37 |

Calculation of the iron requirements of a hypothetical patient by a second method might serve to clarify the formula. Let us assume a hemoglobin concentration of 9 gm. per cent and a blood volume of 4000 ml. The hemoglobin mass for this patient would be 360 gm.

$$9 \times \frac{4000}{100} = 360 \text{ gm.}$$

It should be 540 gm., based on a normal hemoglobin concentration.

$$13.5 \times \frac{4000}{100} = 540 \text{ gm.}$$

The deficit of hemoglobin is 180 gm., so to synthesize this quantity 612 mg. of iron would be required. Add the 500 mg. of iron for storage, and this patient's total requirement is approximately 1100 mg.

### *Route of Administration*

Iron can be administered orally, intravenously and intramuscularly. Under most conditions the oral route is preferred, but parenteral therapy may be justified for some patients. In my experience there are three indications for the use of parenteral iron in obstetrics: (1) intolerance to an oral preparation, (2) absence of iron absorption, or (3) severe anemia near term. Experience with intramuscular iron shows it to be greatly superior to the intravenous preparations, mainly because the side effects are minimal. I question that we have sufficient experience to recommend intramuscular iron for routine administration during pregnancy.

### *Oral Iron Therapy*

Only the ferrous ion is absorbed, so a ferrous salt should be selected. A simple and inexpensive salt such as ferrous sulfate or ferrous gluconate provides adequate iron with a minimum of intolerance. On the basis of available evidence there is no justification for the use of iron salts with other hematinics and vitamins added unless they are specifically indicated. Maximal iron absorption is obtained when the salt is given in divided doses twice or three times a day. The patient should receive 100 to 200 mg. of the element for the day. Thus, 9 gr. of ferrous sulfate or 15 gr. of ferrous gluconate provides adequate amounts of iron. Probably no more than 4 or 5 mg. of the ingested iron can be absorbed. The response to oral iron therapy is gradual because of the limited quantity absorbed. A dramatic reticulocyte response and hemoglobin repair curve should never be expected.

Since all the absorbed iron is utilized for hemoglobin repair, therapy with oral iron salts should be extended well beyond the time when a normal hemoglobin concentration is reached. Only in this way will iron be provided for storage. Illustrated in figure 4 is a typical re-

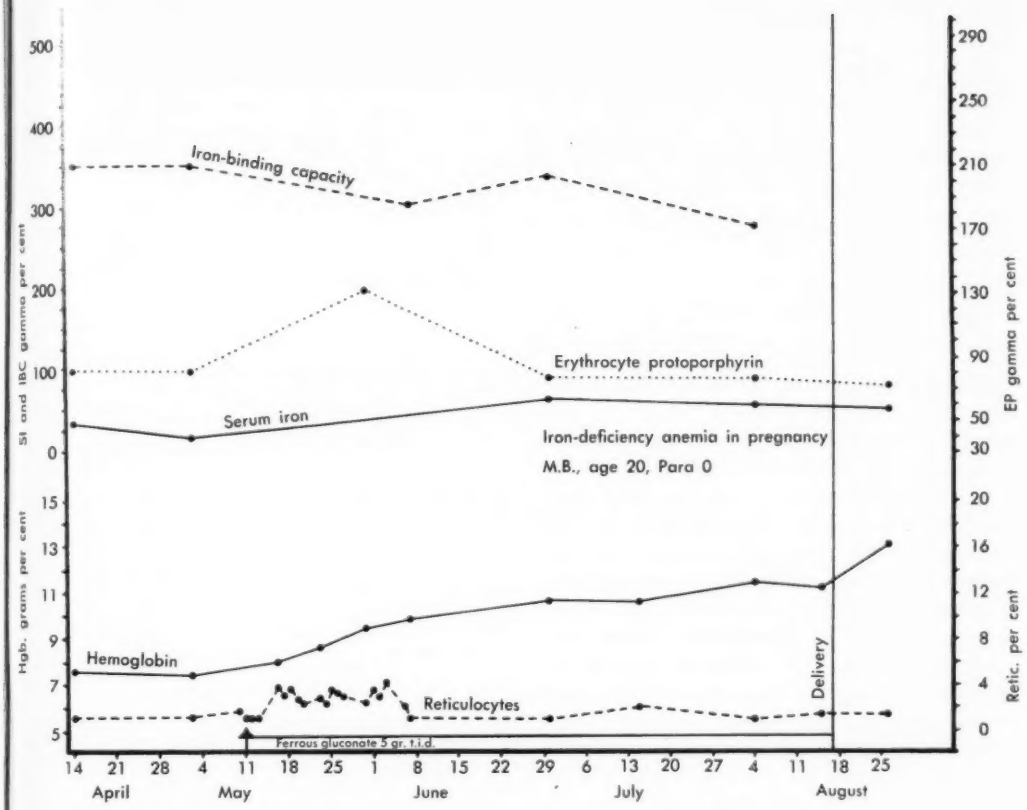



FIGURE 4. Typical response to oral iron by a pregnant patient with severe iron-deficiency anemia.

sponse to oral iron by a pregnant patient with severe iron-deficiency anemia.

I would advocate the routine administration of oral iron to all pregnant patients. Only in this way can anemia be prevented and the iron requirements of the fetus be met without depleting the mother's reserves. A comparison of the results of iron therapy during pregnancy with a group of untreated patients is shown in table 3.

### *Intramuscular Iron Therapy*

Under circumstances where rapid hemoglobin repair may be necessary or where an iron salt is poorly tolerated or absorbed, the need for a parenteral iron is obvious. The better of the two methods seems to be the intramuscular injection, by means of which a maximal amount of iron can be placed within the body pool for utilization by the bone marrow. Our clinical experience has shown the intramuscular injection of iron to be a safe method with relatively few side effects.

Table 4 summarizes the hematologic results

TABLE 4

RESULTS OF ADMINISTRATION OF INTRAMUSCULAR IRON (1000 MG.) TO 75 NORMAL PREGNANT PATIENTS

| | MEAN HEMOGLOBIN (GRAMS PER 100 ML.) | MEAN HEMATOCRIT (PER CENT) |
|---|---|---|
| Pretreatment | 11.4 | 36 |
| Predelivery | 12.1 | 39 |
| Post partum | 12.9 | 41 |



UNIVERSITY OF MICHIGAN LIBRARIES

TABLE 5

RESULTS OF ADMINISTRATION OF IRON TO 26 IRON-DEFICIENT PATIENTS

| | MEAN HEMOGLOBIN (GRAMS PER 100 ML.) | MEAN HEMATOCRIT (PER CENT) |
|---|---|---|
| Pretreatment | 9.2 | 31 |
| Predelivery | 10.9 | 36 |
| Post partum | 12.0 | 39 |

obtained when 1000 mg. of intramuscular iron was administered to a series of normal pregnant patients. Table 5 gives the results in a series of pregnant subjects with anemia. The majority of the normal patients maintained adequate blood values. In no instance did the addition of 1000 mg. of iron overload the patient. The mean results were comparable to those obtained when oral iron was used. When anemia existed, the hemoglobin repair was most often rapid and dramatic. Typical responses in a patient near term and in another patient post partum are given in tables 6 and 7. The response from 9.8 to 11.3 gm. per cent (table 6) within two weeks was gratifying, for transfusions with whole blood were not necessary. The postpartum patient (table 7) illustrates the use of the intramuscular iron in a role common in our experience. Many of our clinic patients deliver without prenatal care and seldom return for postpartum examination. We commonly give these patients intramuscular iron because it replaces whole blood and we know their cooperation with oral iron would be minimal. The hematologic response

TABLE 6

TYPICAL RESPONSE TO IRON THERAPY IN PATIENT NEAR TERM*

| DATE | HEMOGLOBIN (GRAMS PER 100 ML.) |
|---|---|
| April 10, 1957 | 9.8 |
| April 23, 1957 | 11.3 |

*Patient M. C.; estimated date of confinement, May 7, 1957; dose, 1000 mg.

TABLE 7

TYPICAL RESPONSE TO IRON THERAPY* POST PARTUM

| DATE | HEMOGLOBIN (GRAMS PER 100 ML.) |
|---|---|
| December 11, 1956 | 7.4 |
| December 20, 1956 | 10.1 |
| December 27, 1956 | 11.1 |
| April 9, 1957 | 13.1 |

*Dose, 800 mg.

in this one instance in which observations were obtained was dramatic and complete.

Experience with the iron-dextran complex has demonstrated that it can be safely administered in doses from 250 to 500 mg. The dose at each injection site is limited to 5 ml. or 250 mg. Staining is the common sequela and can be avoided by using the Z track injection technic. After drawing the iron preparation into the syringe, a clean needle should be used for the actual injection. It is our practice to inject 0.5 cc. of air after the injection to clear the needle before removing it.

*The physician should be alert to the development of jaundice in the newborn infant. A high concentration of serum bilirubin may cause injury to the brain. Blood group incompatibility, infection, hepatitis or congenital anomalies of the biliary tree may result in the development of jaundice. Other less well-known factors also may be responsible. At present, replacement transfusion is the only satisfactory treatment.*

# Neonatal Jaundice and Prevention of Bilirubin Encephalopathy

WILLIAM J. WATERS*

*State University of New York Upstate Medical Center, Syracuse*

WILLIAM J. WATERS

JAUNDICE in a newborn infant may no longer be considered physiologic or innocuous. Evidence is rapidly accumulating that a satisfactory explanation may be obtained if searched for diligently and that a high concentration of serum bilirubin may cause damage to the brain of newborn infants.

### *Etiology*

The concentration of serum bilirubin in a newborn infant depends on many factors, but it primarily depends on the amount of red cell destruction and, subsequently, on the ability of the liver and possibly other tissues to handle bilirubin (figure 1). The exact methods for evaluating the efficiency of these two processes are not available at the present time.

Serial determinations of the value for the hemoglobin, the hematocrit reading, the reticulocyte count, and the number of nucleated erythrocytes will give some indication of the degree of red cell destruction but probably are inadequate for this purpose. It is also possible that bilirubin may be derived from other heme compounds in the tissues of a newborn infant. Furthermore, from clinical data obtained in my cases, it is suggested that there may be only minimal production and clearance of bilirubin in utero.

Jaundice per se reflects the impairment of tissues of newborn infants to handle bilirubin, and, since the discovery by Billing and Lathe[1] and Schmid[2] that bilirubin is conjugated as a glucuronide, much work has been done in trying to evaluate the effectiveness of this mechanism in newborn infants (figure 2). In this figure, it will be seen that knowledge concerning uridine diphosphoglucuronic acid (UDPGA) and its precursors as well as the activity of transferase and possibly other en-

*Department of Pediatrics, State University of New York Upstate Medical Center, Syracuse, New York.



UNIVERSITY OF MICHIGAN LIBRARIES

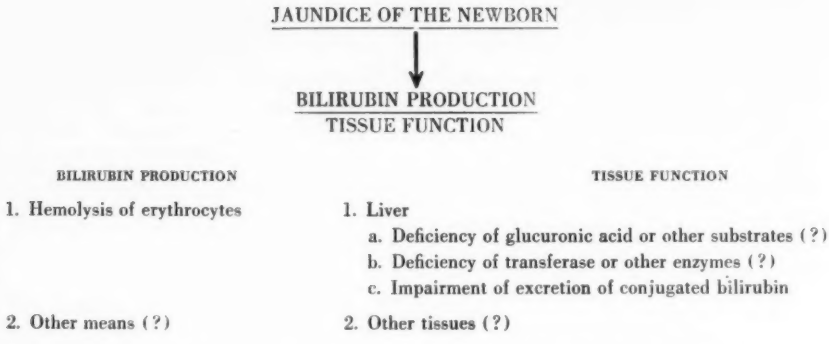

JAUNDICE OF THE NEWBORN
BILIRUBIN PRODUCTION
TISSUE FUNCTION
BILIRUBIN PRODUCTION
1. Hemolysis of erythrocytes
2. Other means (?)
TISSUE FUNCTION
1. Liver
a. Deficiency of glucuronic acid or other substrates (?)
b. Deficiency of transferase or other enzymes (?)
c. Impairment of excretion of conjugated bilirubin
2. Other tissues (?)

FIGURE 1. Schematic representation of the development of jaundice in newborn infants.

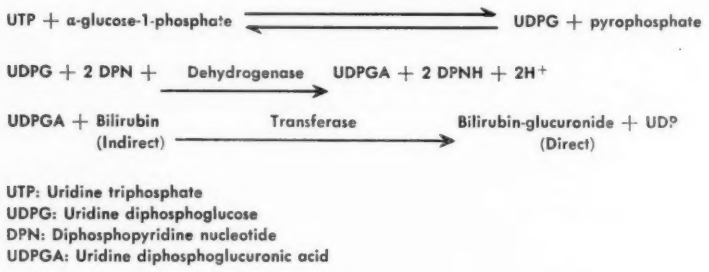



FIGURE 2. Schematic representation of the conjugation of bilirubin.

zymes in the newborn infant is necessary in order to evaluate the role of liver function in this regard.

Lathe and Walker[3] examined liver slices obtained from two newborn infants within a few minutes after their death, but they did not detect any transferase activity. Dunham and I[4] studied a specimen of liver obtained when an operation was performed on a 30 hour old infant. By using a homogenate, we detected the presence of conjugating ability. We, therefore, concluded that transferase activity is variable in the newborn. It probably is deficient although not necessarily absent.

Lacson and I[5] made a study of the urinary excretion of glucuronic acid by newborn infants. Our study indicated that the production of glucuronic acid in newborn infants was deficient as compared with that in adults (table 1), and it also indicated that the response to hyperbilirubinemia was variable. Newborn infants with hemolytic disease who respond best by excreting increased amounts of glucuronic acid in the urine seemed to clear the bilirubin most efficiently. Mosback and King[6] have produced direct evidence that glucose can be used for the synthesis of glucuronic acid in the conjugated form in animals. As a result of this evidence, we arbitrarily have been feeding glucose water as tolerated to jaundiced infants at the State University of New York Medical Center, particularly during the first few hours of life.

Two illustrative cases of jaundice in the newborn suggesting a deficiency of substrate as the mechanism are shown in table 2. On referral, complete studies regarding blood group incompatibility and sepsis were negative, but urinary glucuronic acid values were found to be lower than normal. Thus a diagnosis of hyperbilirubinemia of the newborn was made. By contrast, in the other two cases the presence of biliary atresia was proved, and there was a marked increase in urinary

TABLE 1

AVERAGE EXCRETION OF GLUCURONIC ACID IN THE URINE

| | MG. IN 24 HR. | MG. PER CC. | MG. PER LB.* | MG. PER SQUARE METER† |
|---|---|---|---|---|
| Newborn infants | 13.0 | 0.17 | 1.9 | 56.5 |
| Premature infants | 12.9 | 0.12 | 2.9 | 56.0 |
| Hemolytic disease of the newborn | | | | |
| Conservative treatment | 14.6 | 0.27 | 1.8 | 63.4 |
| Exchange transfusion | 31.1 | 0.42 | 4.4 | 135.1 |
| Adults | 616.5 | 0.51 | 3.3 | 385.2 |

*Of body weight.

†Of body surface.

TABLE 2

DIFFERENTIAL VALUES OF GLUCURONIC ACID IN THE URINE OF INFANTS WITH JAUNDICE

| CASE | AGE | SERUM BILIRUBIN (*Mg. per 100 cc.*) | | EXCRETION OF GLUCURONIC ACID | | DIAGNOSIS |
|---|---|---|---|---|---|---|
| | | *Direct-reacting (Conjugated)* | *Indirect-reacting (Free)* | *Mg. per cc.* | *Mg. in 24 hr.* | |
| ♂ C | 5 days | 1.05 | 17.85 | 0.08 (0.17)* | 9.9 (13.0)* | Hyperbilirubinemia of newborn |
| ♂ F | 5 to 8 days | 1.0 | 19.4 | 0.10 (0.17)* | 5.2 (13.0)* | Hyperbilirubinemia of newborn |
| ♂ M | 7 weeks | 6.0 | 6.0 | 1.5 | 408.0 | Biliary atresia |
| ♀ S | 4 months | 5.3 | 2.2 | 0.65 | 136.5 | Biliary atresia |

*Normal value.

glucuronic acid excretion, which was to be expected.

Jaundice of the newborn may be partly due to a deficiency of substrate or substrates, to a deficiency of enzyme or enzymes, or to a deficiency of both. In some cases, increased amounts of conjugated bilirubin (direct-reacting bilirubin) will be found in the serum early in the course of the jaundice, and will suggest a further defect in the excretion of this substance by the liver cells (figure 1). Beyond the neonatal period, the presence of this type of hepatic defect is further suggested by the occurrence of the Dubin-Johnson syndrome, in which the value for the conjugated bilirubin is increased.

### *Clinical Course*

Clinically, one should be alert to the development of jaundice in the newborn, particularly within the first 12 to 24 hours of life. High concentrations of serum bilirubin may occur in infants of this age and may cause injury of the brain unless efforts are made to prevent it. It should be emphasized that jaundice is rarely present at birth, and by the time it becomes visible the value for the serum bilirubin usually is at least 4 to 6 mg. per 100 cc. Determination of the concentration of serum bilirubin in the blood of the umbilical vein is advantageous in a case in which hemolytic disease is likely to develop. If the value for the serum bilirubin in the blood of the umbilical vein is more than 3.5 mg. per 100 cc., it suggests impending difficulty, and it should be rechecked within a few hours even if the infant appears to be well.

Figure 3 shows projected curves for the concentration of serum bilirubin in the blood of newborn infants with jaundice. In most



UNIVERSITY OF MICHIGAN LIBRARIES

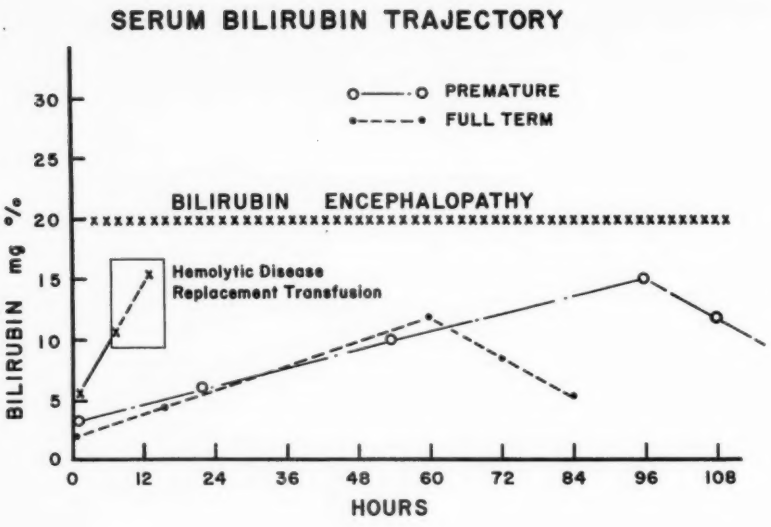



FIGURE 3. Projected curves for the concentration of serum bilirubin in newborn infants with jaundice. The critical level is designated as greater than 20 mg. per 100 cc.

cases, the jaundice does not become apparent until the second day, and the highest concentration of serum bilirubin occurs at the age of 48 to 72 hours. Thereafter, the concentrate becomes stabilized or decreases progressively. In a premature infant, however, the concentration usually reaches its peak somewhat later. Under ordinary circumstances, the concentration rarely exceeds 20 mg. per 100 cc., but it occasionally may do so. Therefore, in following the clinical course of the disease, the concentration of serum bilirubin should be determined repeatedly.

In cases of hemolytic disease of the newborn, the concentration of serum bilirubin may increase rather rapidly after birth. In a case in which the infant was Rh positive and the Coombs test was positive, the concentration of serum bilirubin in the blood of the umbilical vein initially was 5 mg. per 100 cc., but it increased to more than 10 mg. per 100 cc. by the time the infant was six hours old (figure 3). A further rapid increase can be anticipated, as illustrated by the dotted line in the rectangle, and, by the time the peak concentration might be reached, the concentration should be well over 20 mg. per 100 cc. Therefore, a replacement transfusion is indicated early in order to prevent brain damage. The effectiveness of this procedure in reducing the incidence of brain damage cannot be denied, but its entire mode of action is not clear. Further investigation of this effect of replacement transfusion is urgently needed.

### *Differential Diagnosis*

Blood group incompatibility, commonly on an ABO or Rh basis, rarely on other groups, probably accounts for a significant number of instances of jaundice in newborn infants. Therefore, this should be searched for promptly by appropriate procedures in a case in which a newborn infant is jaundiced.

The possible presence of infection, particularly bacteremia, should be considered, and a search should be made for infection. A high index of suspicion, the use of blood cultures, and the subsequent institution of appropriate treatment may be lifesaving in cases in which infection is present. The possible presence of less common entities, namely, syphilis, toxoplasmosis and cytomegalic inclusion disease, may have to be considered. The presence of hepatitis and congenital anomalies of the biliary tree may have to be excluded by appropriate studies as well as by repeated observation. A tumor, either primary or metastatic, rarely may be found in infancy.

Aside from these well-recognized clinical entities, recent work has indicated that sev-

eral other factors may be responsible for jaundice in newborn infants. The administration of SYNKAYVITE® (vitamin K) in large doses (30 mg. or more) has been shown to have been associated with an increased incidence of jaundice and brain damage.[7,8] The results of recent studies in our laboratory[9] would suggest that Synkayvite may inhibit the conjugation of bilirubin. Previous work would suggest that it also may cause hemolysis of the red cells of newborn infants.[10] Jaundice, therefore, might result from either or both of these mechanisms. Our present policy at the medical center is to administer a single dose of 1 mg. of Synkayvite to the infant as a prophylactic measure after birth. In hospitals in which it is the practice to administer Synkayvite to the mother prior to delivery, the dose should be extremely small or perhaps the administration of this preparation should be discontinued.

GANTRISIN® has been implicated as a cause of an increased incidence of brain damage in premature infants with jaundice,[11] but the exact manner in which it causes this increase is not clear. This drug, however, should not be used in the treatment of a newborn infant who has jaundice.

An increase in the degree of jaundice has been observed in premature infants who have respiratory difficulty in the first hours of life.[12] An investigation should be made to determine whether this increase is related to anoxia or to the administration of oxygen. Finally, an association between neonatal jaundice and hypothyroidism has been suggested.[13]

### *Treatment*

A previous study has convinced me that the antibody titer and a positive Coombs test by themselves are not an indication for a replacement transfusion in the newborn.[14] These tests indicate that the mother has been sensitized and that the infant's red cells have been coated with antibody, but a number of these infants will do well clinically without a replacement transfusion. However, close clinical supervision is essential, and frequent determinations of the value for the serum bilirubin may be necessary. In cases in which obvious signs of disease (pallor, hepatomegaly, ecchymosis and edema) are present at birth, a replacement transfusion should be administered promptly. On the other hand, if the child is well clinically, a replacement transfusion should not be administered unless repeated determinations reveal an impending rapid increase in the value for the serum bilirubin. Replacement transfusion is not without danger, particularly when it is administered by unskilled personnel. Infants who are to receive a replacement transfusion should be selected carefully, and they should be closely observed after the transfusion has been performed.

In the light of recent knowledge and as a result of a recent report,[15] we have administered sodium glucuronate intravenously early in several cases of jaundice of the newborn, but we have not been able to detect any significant decrease in the concentration of serum bilirubin as a result of the administration of this drug. Therefore, the routine use of this drug is not recommended at present.

### *Summary*

Jaundice that occurs in newborn infants requires explanation, and an etiologic appraisal should be made in order to care for the infant effectively. In a case in which jaundice develops early, particularly within 12 hours after birth, treatment probably will be required in order to prevent brain damage. At present, replacement transfusion is the only satisfactory treatment.

Further knowledge concerning the metabolism of bilirubin in the fetus and the newborn is needed. Such knowledge may result in more effective methods of treatment. In the light of present knowledge, drugs and other forms of treatment should be carefully re-evaluated in pregnancy and in the neonatal period. It is essential to avoid the use of those that may be detrimental.

### REFERENCES

1. BILLING, B. H. and LATHE, G. H.: Excretion of bilirubin as an ester glucuronide, giving the direct van den Bergh reaction. Proc. Biochem. Soc., Biochem. J. 63:6P, 1956.
2. SCHMID, R.: Direct-reacting bilirubin, bilirubin glucuronide, in serum, bile, and urine. Science 124:76 (July 13) 1956.



UNIVERSITY OF MICHIGAN LIBRARIES

3. LATHE, G. H. and WALKER, M.: Enzyme defect in human neonatal jaundice and in Gunn's strain of jaundiced rats. Proc. Biochem. Soc., Biochem. J. 67:9P, 1957.
4. WATERS, W. J. and DUNHAM, R.: Unpublished observation.
5. LACSON, P. S. and WATERS, W. J.: Urinary hexuronic acid determinations in prematures, newborns and young infants. A.M.A. J. Dis. Child. 94:510 (October) 1957.
6. MOSBACK, E. H. and KING, C. G.: Tracer studies of glucuronic biosynthesis. J. Biol. Chem. 185:491 (August) 1950.
7. CROSSE, V. M. and MEYER, T. C.: Prematurity-jaundice-kernicterus syndrome. A.M.A. J. Dis. Child. 90:602 (December) 1955.
8. ALLISON, A. C.: Danger of vitamin K to newborn. Lancet 1:669 (March 26) 1955.
9. WATERS, W. J., DUNHAM, R. and BOWEN, W. R.: Inhibition of bilirubin conjugation in vitro. Proc. Soc. Exper. Biol. & Med. 99:175 (October) 1958.
10. ZINKHAM, W. H. and CHILDS, B.: Effect of vitamin K and naphthalene metabolites on metabolism of erythrocytes from normal newborns and patients with naphthalene hemolytic anemia. A.M.A. J. Dis. Child. 94:420 (October) 1957.
11. SILVERMAN, W. A., ANDERSEN, D. H., BLANC, W. A. and CROZIER, D. N.: Difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens. Pediatrics 18:614 (October) 1956.
12. MILLER, C. A. and REED, H. H.: Relation of serum levels of bilirubin to respiratory function of premature infants. A.M.A. J. Dis. Child. 94:517, 1957.
13. AKERREN, Y.: Prolonged jaundice in newborn associated with congenital myxedema; syndrome of practical importance. Acta paediat. 43:411, 1954.
14. WATERS, W. J.: Prevention of bilirubin encephalopathy. J. Pediat. 52:559 (May) 1958.
15. DANOFF, S., GRANTZ, C., BOYER, A. and HOLT, L. E., JR.: Conversion of indirect- to direct-reacting bilirubin in vivo. Science 127:759 (April 4) 1958.

PANEL DISCUSSION

**Emergencies in the First Day of Life**

WILLIS J. POTTS, M.D.
(Moderator)

Professor of Pediatric Surgery, Northwestern University Medical School, and Surgeon-in-Chief, The Children's Memorial Hospital, Chicago

JOHN L. REICHERT, M.D.

Assistant Professor of Pediatrics, Northwestern University Medical School, Chicago

PAUL H. HOLINGER, M.D.

Clinical Assistant Professor of Broncho-esophagology, University of Illinois College of Medicine, Chicago

1959

**INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY**

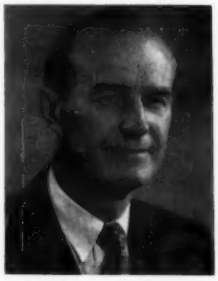
Nov. 2-5 Palmer House Chicago, Illinois

# Juvenile Eczema: Atopic Dermatitis

LOUIS A. BRUNSTING*

*Mayo Clinic and Mayo Foundation, Rochester, Minnesota*

*Atopic dermatitis in young people may be mild or generalized and disabling. Its etiology is obscure, but a combination of factors including allergic features, vascular imbalance and psychosomatic disturbances seems to be involved. While conventional allergic therapy has little practical value, rest, moderation of activities, change of residence, and corticosteroid therapy may produce improvement. Treatment of the skin alone, without giving due consideration to the over-all picture, will invariably be unsuccessful.*



LOUIS A. BRUNSTING

To regard eczema as a simple subject is beguiling for, in spite of its antiquity, the mechanism of the disease is still quite controversial. For practical purposes, I shall limit my comments to the phase of chronic eczema as it appears in adolescents and young adults under the name of "atopic dermatitis." Most family physicians are familiar with the clinical picture and with the misery and disability engendered by this common disorder; to dermatologists it is a chronic headache.

It is well recognized, by physicians and laymen alike, that the person with atopic dermatitis is a peculiar individual. Some of these peculiarities are inborn, while others, no doubt, are acquired as a result of the load of this chronic, baffling disability throughout the formative years of life. Nor is the family spared. In this disease, the problems of the skin are compounded by the problems of the teen-ager; and all too often the parents, especially the mother, are caught up in the web. Any program of management that fails to take into account the complex factors which make up the background of the atopic state is doomed to failure from the start. A small booklet[1] on this subject, a symposium comprising the opinions of experts in this field, is available and is heartily recommended.

### *Definition*

The term "atopic dermatitis" was coined about 25 years ago by Coca and co-workers,[2] and its common usage was furthered by Sulzberger[3] to give a meaningful name to the dis-

*Section of Dermatology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Presented before the forty-third annual Assembly of the Interstate Postgraduate Medical Association at Cleveland.



UNIVERSITY OF MICHIGAN LIBRARIES

tinctive type of chronic lichenified eczema which appears in persons in infancy, childhood, adolescence or even in later years in association with so-called atopic stigmas such as asthma or hay fever in themselves or in their families. There is no counterpart of this disease found in animals. Urticarious reactions to skin tests, circulating reagins and eosinophilia can be demonstrated.

Earlier observers, especially those from Europe, had recognized the peculiar diathesis involved in the process (prurigo diathesique, status exudativus), the association with asthma and hay fever, and the hyperkinetic nervous qualities of the patients. The term "neurodermatitis" was used indiscriminately. The British still favor the name "Besnier's prurigo."

In this country, usage seems to have decreed that the name "atopic dermatitis" shall stand, even though the original implications of the term have had to be modified. For example, arguments ensue over the importance of psychosomatic factors or over the validity and specificity of data obtained by surveys of various allergies.[4-6] Atopic dermatitis stands apart from contact dermatitis, seborrheic dermatitis and drug eruptions. I believe that atopic dermatitis represents an inborn defect of the skin and probably of the autonomic nervous system as well, although, as of today, evidence for the latter is largely presumptive.

### *Clinical Pattern and Course*

More than half of the young adults with atopic dermatitis had eczema in infancy. Now and then, the process has remained without interruption, but usually two or three phases occur: in infancy for two years, in the early grade-school years, and again in early adolescence. The summer months often produce remissions; the eruption returns with the advent of fall, and it is worst of all during the winter months. Spontaneous remissions are not uncommon, and these may last for months or years. In persons after the age of 25, the process usually abates, except in the more intractable instances in which the entire body is often involved and the patient is completely disabled.

Itching, lichenification and chronicity are the hallmarks of atopic dermatitis. Itching may arise from thermal, emotional or allergic stimuli or for no apparent reason, and may be out of proportion to the eruption. In fact, itching is usually the first symptom. It may be steady, but more often it is paroxysmal in character; commonly it occurs during the first hour of sleep. When the patient is awakened or distracted, the itching may pass.

In infancy, the eruption of atopic dermatitis is usually moist and exudative and chiefly affects the cheeks, the scalp and the extremities. In childhood, the flexural surfaces of the arms and the face are involved with typical areas of lichenification, or a prurigo type of papular eruption may appear on the extensoral surfaces of the extremities. In older persons, the sites of predilection are the eyelids, face and neck, the cubital and popliteal fossae, the wrists and the genitalia. Here, lichenification is invariably present; the process may assume generalized proportions. In such cases, hyperpigmentation occurs, sometimes to a remarkable degree, depending on the complexion. In acute cases, excoriations abound; in chronic cases, cutaneous effects seem to develop as a result of rubbing the skin. Often the hair of the outer third of the eyebrows has been rubbed away. Lymphadenopathy of variable degrees may be present and sometimes, in severe cases, may assume such proportions that the diagnosis of lymphoma must be entertained.

Patients with atopic dermatitis often exhibit a peculiar waxy pallor which is distinctive to the experienced observer. This may be limited to the tip of the nose or to the face and the other sites involved, or it may be generalized. Often the face, especially after exposure to cold or after a strong emotional stimulus, assumes a dead-white, alabaster hue. In some persons, this may persist more or less as a permanent mark of the disease. The explanation for this unusual phenomenon may lie in the lability of the capillaries, which in these cases are in a permanent state of constriction.

### *Associated Stigmas*

Most peculiarities associated with atopic dermatitis have been enumerated by Kierland.[7] Some of these are related to the im-

n unologic response, such as the association with asthma, hay fever, vasomotor rhinitis and, sometimes, urticaria and migraine. The urticarious whealing response to cutaneous testing with protein allergens of foods, pollens, molds and dusts has been mentioned, and, likewise, the presence of circulating reagins and eosinophilia.

The skin itself is abnormal in such patients. Vitiligo and alopecia are not infrequent concomitants. The skin is invariably dry and often shows evidence of keratosis pilaris. Actual ichthyosis may be present. These factors contribute to faulty delivery of sweat which, in turn, may set off paroxysms of itching during hot and humid weather or after physical exertion. Contact with wool and with dusts is poorly tolerated.

Patients with atopic dermatitis manifest a number of physiologic abnormalities which seem to reflect autonomic imbalance. Stroking the skin produces white dermographia, and the cutaneous response to intradermally injected histamine or acetylcholine differs from the normal response. Measurements of the temperature of the fingers and toes and of the skin at the sites most frequently involved by the eruption indicate an exaggerated and prolonged reaction to thermal stimuli, particularly to cold. A tendency to hypotension is usually present, but at the same time the response to the cold pressor test is hyperreactive. The curve of the glucose tolerance test is inclined to be flat. The level of histamine in the blood, usually quite constant in normal persons, tends to fluctuate unpredictably in patients with atopic dermatitis, and such changes seem to be correlated more closely with the number of basophils than with eosinophils.

These persons have two inexplicable peculiarities which should be mentioned: (1) Ocular complications have a tendency to develop in more than a small number of them in early adolescence in the form of cataracts and, sometimes, keratoconus, and (2) violent cutaneous and constitutional reaction is manifested by the group as a whole to infection by the virus of vaccinia and of herpes simplex.

Finally, a word or two about a highly controversial issue, the so-called personality pattern of the atopic patient. There are those who deny categorically any psychogenic relationships. There are others who can see nothing else in the picture. My own viewpoint has been well expressed by O'Leary.[8] I am convinced that these persons have an irritable nervous system as well as an irritable skin; they are restless spirits by inheritance. This is not due to the itching alone. Even during periods of relative remission they react excessively to stressful situations, such as those induced by anger, frustration, argument, semester examinations and love affairs. Fatigue is a natural counterpart, although it may be subdued or suppressed as Becker and Obermayer[9] have pointed out. In long-standing cases it is only natural that certain dependent or defensive complexes should develop as a consequence.

### *Treatment*

In the light of present knowledge, the treatment of atopic dermatitis is purely empiric. The ideal situation, impractical as it may be, is one in which allergic insults and competitive and stressful stimuli are reduced to a minimum and the patient lives in a climate that best suits his particular skin.

Fortunately, the naïve trust so long placed in the efficacy of the conventional technics, e.g., tests, diets and injections, of the allergist in controlling or curing the disease is gradually being dissipated. Most dermatologists agree that the allergic approach has little practical value. Common sense will guide the patient in eliminating foodstuffs that provoke unpleasant sensations or in avoiding contact with external factors which irritate the skin. Dietary restrictions should never be carried to the point of jeopardizing nutritional balance. I have never seen a diet cure a patient with atopic dermatitis.

If a program of adequate rest and moderation of activities can be enjoined, the battle is half won. Unfortunately, this adolescent, not being particularly sick in the ordinary sense, resents any attempt to restrict or cramp his style and is inclined to become rebellious. From early childhood he has been dynamic and overstimulated; he carries an overloaded schedule and seeks constant diversion to dis-



UNIVERSITY OF MICHIGAN LIBRARIES

tract him from his itch. Perhaps this overactivity is related in an obscure way to his allergic mechanism; the same restlessness characterizes the experimental animal undergoing the early stages of mild anaphylactic reaction. Situations of tension should be avoided or compromised; schooling may need to be interrupted for a year or more rather than for a few weeks; a reasonable prospect should be set on an ambitious career, and family turmoil should be unraveled. As a rule, these problems are better handled by the sympathetic counseling of the family physician than by the professional analyst.

It has been known for some time that patients with atopic dermatitis are improved by a change of residence, particularly to an arid climate where they may enjoy sunshine the year around. If such a change is deemed advisable, it should be carried out before the pattern of living is too firmly established. It is my experience that such persons do better in the vicinity of Arizona than in California or Florida. Not all patients are improved, nor is it easy to explain why so many are benefited. Naturally, many factors are involved in pulling up roots, and it would be fatuous to ascribe the results of such change to climate alone.

A word about corticosteroid therapy for atopic dermatitis is in order. The striking relief of symptoms produced by the administration of cortisone preparations and ACTH was noted soon after these hormones were introduced. The early enthusiasm, however, was tempered as soon as physiologic reactions and complications became apparent. In the past decade there has been an encouraging succession of newer products, somewhat refined of side effects and capable of controlling symptoms in a lower concentration than before; but these are still not without hazard in the long run. The patient with atopic dermatitis naturally is delighted with a simple form of treatment which will relieve his symptoms and improve his sense of well-being, but in chronic cases this satisfaction more often than not is delusional and short-lived. Although it would be desirable to be able to regulate dosage to meet the inevitable ups and downs of the disease, at present I find this impractical. Anyone who initiates such a program of treatment should be prepared to accept responsibility for maintenance, for appreciating unfavorable side effects, and, particularly, for managing the problems incident to the withdrawal of the hormones.

Other drugs which are useful in relieving symptoms are few in number. Antihistaminics are partly effective; acetylsalicylic acid is not to be overlooked. The best soporific at bedtime is chloral hydrate. A sedative such as phenobarbital is time-tried and valuable in relieving nervous irritability but is apt to be depressing. The early promise of the tranquilizers has not been fulfilled. During the acute stages of atopic dermatitis, large doses of chlorpromazine may deaden the sensibilities but not for long; I am told by psychiatrists that the use of tranquilizers by ambulatory neurotics is quite without benefit. Combinations of phenothiazine derivatives and antihistaminics are useful in some cases, but the inherent dangers should not be overlooked. For controlling the severely paroxysmal seizures of pruritus in stages of exacerbation, there is nothing better than ACTH administered by intravenous drip; two or three such treatments spaced a few days apart give time for more conventional measures to take hold.

From the standpoint of the treatment of the skin, I shall first say something about measures that should be used with caution. I have never favored the use of roentgen therapy for, as in most chronic recurring conditions, the limit of tolerance is soon realized. Countless eczema "cures" have been marketed for the relief of pruritus. Because of their sensitizing potential, care should be used in prescribing preparations which depend for their effect on the presence of local anesthetics or antihistaminics. The same is true of the ointments or lotions containing antibiotics. In spite of constant trauma, the skin of these patients is rarely infected. If pyogenic infection does develop, treatment should be carried out according to modern bacteriologic principles.

Patients with atopic dermatitis profit by rest which, if the involvement of the skin is widespread, is preferably carried out in the hospital. Baths with oatmeal or starch powder

added are quite soothing. If the skin is dry, a miscible, oily preparation is added to the bath. During the stage of acute inflammation, moist compresses are effective. These may be used intermittently for several days, being changed at intervals of three or four hours. Moist but not soaking wet dressings should be applied, and impermeable outer coverings should not be used. Probably the most commonly used solutions are wet dressings of diluted aluminum subacetate or liquor d'Alibour.

As soon as the acute stage is passed, ointments are applied. At first a simple preparation such as petrolatum, perhaps with the addition of 1 or 2 per cent salicylic acid, is used. In this group of patients the tars, either pine tar or crude coal tar, are tolerated rather well. Their therapeutic value outweighs the messiness. If tar ointments are found to be agreeable, I add exposure to ultraviolet rays daily in increasing doses until the patient has received an over-all tan.

Lately in treating these patients, hydrocortisone or its derivatives have been added to ointments and lotions with somewhat remarkable symptomatic effects. At present, the expense of such preparations more or less prohibits their use over a widespread area for long periods. In any case, in view of the chronic nature of the disorder, it is necessary to change medicaments from time to time, since various preparations outwear their usefulness.


### *Summary*

Atopic dermatitis is a complex disorder, probably based on an inherited abnormality of the skin and the nervous system. The etiology is obscure. A combination of factors including allergic features, vascular imbalance and psychosomatic disturbances seems to be involved. Treatment of the skin alone, without giving due consideration to the over-all picture, will invariably be unsuccessful.


### REFERENCES


1. Baer, R. L. (ed.): Atopic Dermatitis. Philadelphia, J. B. Lippincott Company, 1955.
2. Coca, A. F., Walzer, M. and Thommen, A. A.: Asthma and Hay Fever in Theory and Practice. Springfield, Illinois, Charles C Thomas, 1931.
3. Sulzberger, M. B.: Atopic dermatitis: Its clinical and histologic picture. In Baer, R. L. (ed.): Atopic Dermatitis. Philadelphia, J. B. Lippincott Company, 1955, pp. 11-42.
4. Tuft, L.: Correspondence. J. Allergy 27:293-294 (May) 1956.
5. Hill, L. W.: Atopic dermatitis. J. Allergy 27:480-482 (September) 1956.
6. Baer, R. L.: Correspondence. *Ibid.*, pp. 483-484.
7. Kierland, R. R.: Certain stigmata associated with atopic dermatitis. In Baer, R. L. (ed.): Atopic Dermatitis. Philadelphia, J. B. Lippincott Company, 1955, pp. 43-55.
8. O'Leary, P. A.: Atopic dermatitis. South. M. J. 46:67-73 (January) 1953.
9. Becker, S. W. and Obermayer, M. E.: Modern Dermatology and Syphilology. Ed. 2. Philadelphia, J. B. Lippincott Company, 1947.


UNIVERSITY OF MICHIGAN LIBRARIES

*A close interrelationship exists between lymphoma and leukemia. In some cases diagnosis requires specimens of lymph node, bone marrow and blood. Life expectancy can be more accurately anticipated in leukemia than in cases of lymphoma. With presently available therapeutic agents, carefully planned, persistently pursued treatment may result in prolonged survival.*

# Newer Aspects in the Diagnosis and Treatment of Lymphomas and Leukemias

EDWARD SHANBROM*

*Orange County General Hospital, Orange, California*

EDWARD SHANBROM

THE study of the lymphomas and leukemias has become of widespread interest in recent years. These diseases are not as rare as they formerly were thought to be, nor is the prognosis always as dim as it is generally held for all these conditions. The increasing exposure of the general population to radioactive materials has given great emphasis in recent years to the study of the leukemias. It is impossible to cover all aspects of these diseases with any degree of completeness in one article, and since a general review of the subject can easily be found in any of the standard textbooks of hematology I shall attempt only to present some current concepts and newer approaches to treatment of these disorders.

### *Classification*

The lymphomas are generally classified as:

1. Reticulum cell sarcoma (figure 1).
2. Lymphosarcoma, of which there are two varieties, immature or lymphoblastic type (figure 2) and small cell or lymphocytic type.
3. Giant follicular lymphoma (figure 3), which is also referred to as giant follicular lymphosarcoma or follicular lymphoblastoma, and finally as hematogonic lymphoma.
4. Hodgkin's disease, probably the most common disease of this group (figure 4). Many hematologists consider that there are three varieties: paragranuloma, the most benign phase; granuloma, the most common form; and sarcoma, a highly malignant phase.
5. A fifth type of lymphoma could be chronic lymphocytic leukemia. Although it generally is classified with leukemias (and I shall discuss it as such), it more probably should be classified as a lymphoma since the disease does begin very often in the lymph node itself

*Former Chief, Lymphoma-Leukemia Section, City of Hope Medical Center, Duarte, California; Associate Chief of Clinical Service, Orange County General Hospital, Orange, California.

Adapted from a presentation at the Second Inter-American Medical Convention, Panama City.

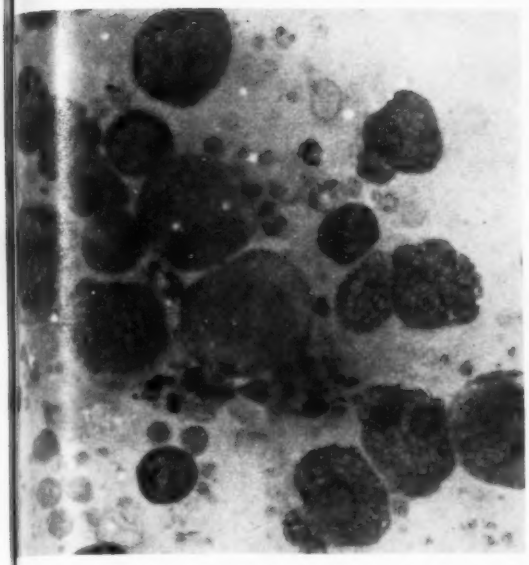


FIGURE 1. Photomicrograph of specimen obtained by aspiration of a lymph node in a case of reticulum cell sarcoma. Size and shape of these cells vary considerably. Nuclear chromatin is rather coarsely reticulated. Nucleoli are unusually prominent.

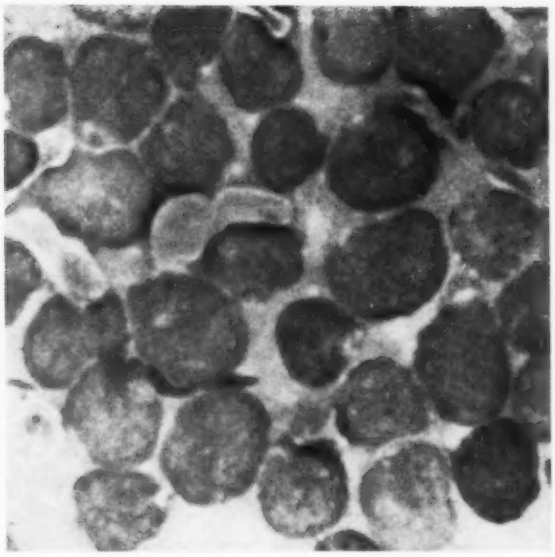


FIGURE 2. Photomicrograph of specimen obtained by lymph node puncture in lymphoblastic lymphosarcoma. Nuclear chromatin is fairly homogenous and poorly organized. Nucleoli are not as numerous or prominent as those in reticulum cells.

and may be confined to this tissue for many years before the bone marrow is involved.

6. Finally, there is the condition known as mycosis fungoides. Most authors classify this as a lymphoma, for ultimately it behaves as such. It remains for many years, however, as a dermatologic condition, sometimes misdiagnosed as exfoliative dermatitis.

Classification of the leukemias is simple, dividing the diseases into the acute and chronic phases. The main divisions are *granulocytic*, *lymphocytic* and *monocytic*. In the granulocytic form one rarely encounters basophilic and eosinophilic leukemias. The monocytic forms are subdivided into the Naegeli type, a mixture of granulocytic and monocytic elements, and the Schilling type, a pure monocytic leukemia. Most of the monocytic leuke-

FIGURE 3. Photomicrograph of specimen obtained by aspiration of a lymph node in a case of giant follicular lymphoma. Under low power the characteristic "hematogones" are easily seen scattered between the other lymphoid elements. They are small mature lymphocytes with homogenous, deeply staining nuclei and scant or no cytoplasm.

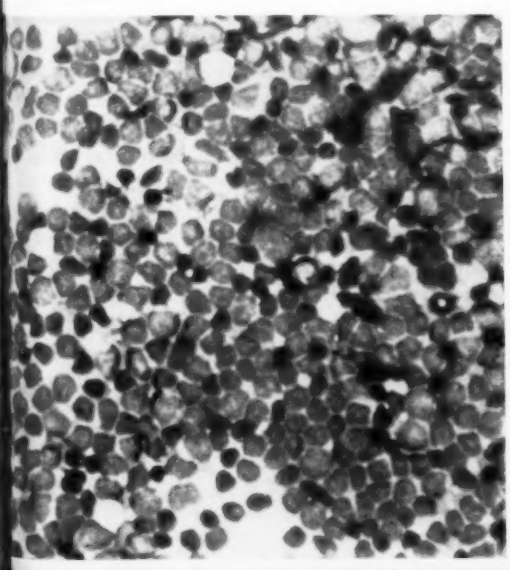
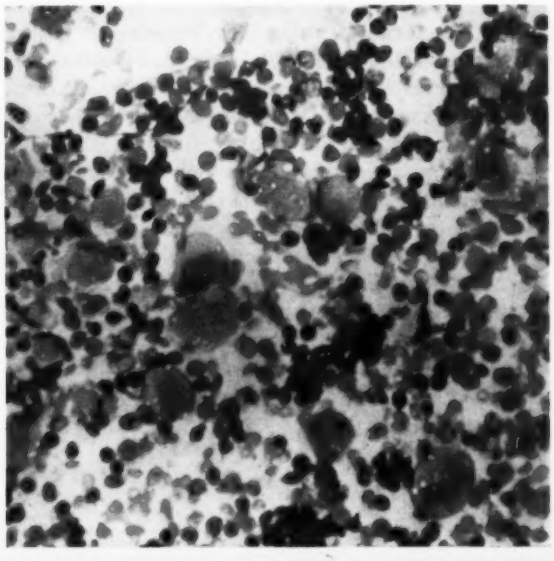


FIGURE 4. Low-power photomicrograph of a specimen obtained by lymph node aspiration in a case of Hodgkin's disease. Note the striking pleomorphism of the cells with numerous giant cells predominating.



UNIVERSITY OF MICHIGAN LIBRARIES

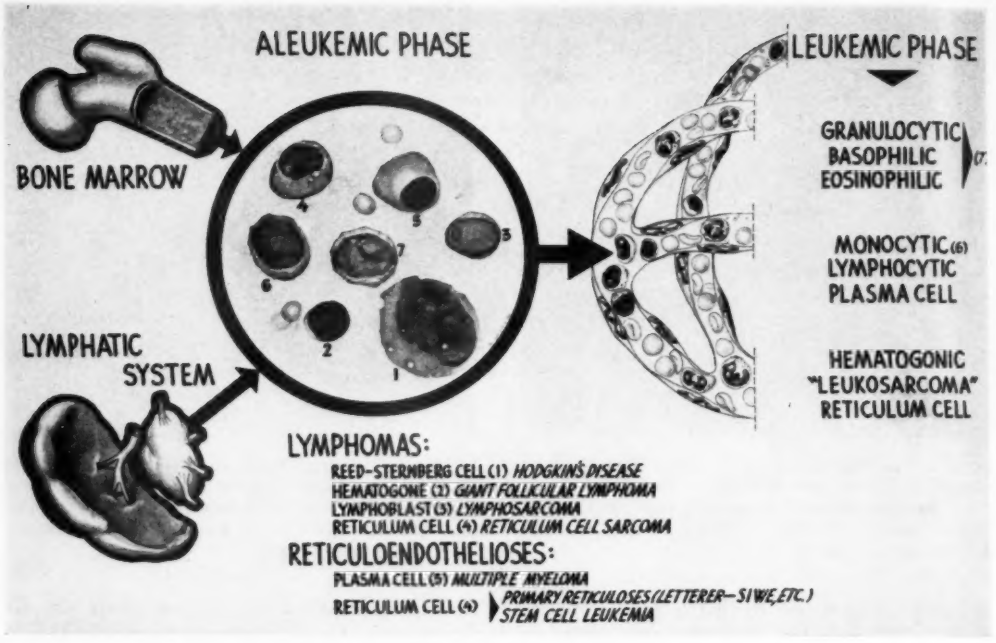



FIGURE 5. Schematic representation of the interrelationship of the reticuloendothelial neoplastic disorders.

mias are acute, but chronic forms have been described.

By definition we usually think of leukemia as meaning an increase of white blood cells or the presence of abnormal forms of white blood cells, or both, in the blood stream. However, in the acute forms there may be a leukopenic and even an aleukemic picture during some phase of the disease process and the disease remains confined to the blood-forming tissues, for the most part the bone marrow. The reasons for this are not clear at this time, but such observations, enforced by other similarities which I shall discuss, have linked the lymphomas and leukemias together. Lymphosarcoma, for example, begins as a disease of the lymph nodes and may remain that way for months or years. In a very high percentage of cases, however, frequently in the terminal phase of the disease, a leukocytosis occurs and an increase in the number of lymphocytes may be found in the peripheral blood. In many cases the picture may resemble a frank leukemia and may be impossible to differentiate from that of chronic lymphocytic leukemia. Such a phase is referred to as "leukosarcoma,"[1,2] and it is only by understanding the natural course of the disease that one is able to distinguish this condition from chronic lymphocytic leukemia.

While many physicians are aware of the so-called leukosarcoma, it is not generally known that there is a leukemic phase of giant follicular lymphoma in which large numbers of small lymphocytes are found in the blood stream. These lymphocytes have been termed "hematogones"[3] and differ from normal lymphocytes in that they have an intensely basophilic homogenous nucleus and scant, if any, cytoplasm. In giant follicular lymphoma these cells predominate in biopsy specimens of lymph nodes obtained surgically or by aspiration, and they may also be found in increased numbers in the bone marrow and blood of patients with this condition. In rare cases reticulum cell sarcoma may produce a leukemic picture and large numbers of reticulum cells may be found in the blood stream. Hodgkin's disease,

in contrast to the other lymphomas, does not exhibit a leukemic phase, although there have been very rare reports of the finding of Reed-Sternberg cells in the peripheral blood,[4] and from time to time one finds reports of Reed-Sternberg cells being recognized in routine bone marrow examination.[5]

The lymphomas and leukemias have many aspects in common. (1) They all appear to be neoplastic or neoplasticlike disorders of the reticuloendothelial tissue. (2) Each of the conditions has a particular cell which is characteristic of the disorder. (3) Each of the conditions has an *aleukemic* phase and exists as a primary tumor of certain reticuloendothelial tissue (figure 5). (4) Each of the disorders, with the exception of Hodgkin's disease, as previously mentioned, may have a leukemic phase in which the typical cell may be found in the blood stream in variable numbers. (5) Although the disease may begin in a specific site of the reticuloendothelial system, eventually all this tissue becomes involved, although there may be a long period in which the disease is apparently confined to one site. This appears to be particularly true of the lymphomas. In the early phase of chronic lymphocytic leukemia, for example, the bone marrow may be entirely normal.[6]

Thus, there is a very close interrelationship between lymphoma and leukemia, and at times it is difficult to say with certainty where one begins and the other ends.

### *Diagnosis*

It is not always realized that specimens of lymph node, bone marrow and blood may be necessary to establish the diagnosis in some cases of lymphoma and leukemia. Whenever possible we attempt to obtain specimens of all three tissues, not only for diagnostic reasons but for a better understanding of the natural pathogenesis of these disorders. Some hematologists feel it is unnecessary to examine the bone marrow in the chronic leukemias, considering the peripheral blood picture adequate for diagnosis. However, it has been our experience that a *leukemoid* response to some other existing condition can be mistaken for a true leukemic picture. Although examination of the peripheral blood usually is adequate for the diagnosis of chronic lymphocytic leukemia, examination of the bone marrow is most helpful not only in understanding the fact that this condition is more closely allied to the lymphomas than to the true leukemias but also as a guide to prognosis, since those cases in which there is little or no involvement of the bone marrow usually have a better prognosis. Whenever a lymph node biopsy is performed it is highly desirable to make a touch preparation of a cut surface of the lymph node. At our institution this is a routine procedure and these touch preparations are stained with both Wright's and Giemsa's stains. By using the same staining technics for lymph nodes, bone marrow and blood, it is now possible to recognize the "leukemic" phase of lymphomas before the leukocyte count of the peripheral blood has become elevated.

Diagnosis of most lymphomas is made with a high degree of accuracy by pathologists. However, Hodgkin's disease, in its early phase, often presents a perplexing problem. On innumerable occasions we have seen patients who have had repeated biopsies of lymph nodes which have been reported simply as chronic hyperplastic nodes, chronic lymphadenitis, or chronic inflammatory changes. If enough biopsies are done, sooner or later in many of these cases the typical Reed-Sternberg cells (figure 6) appear and the diagnosis of Hodgkin's disease is then established.[7] When the clinical condition warrants it, repeated biopsies of enlarged lymph nodes must be done at close intervals if the early diagnosis of Hodgkin's disease is to be established. On the other hand, it cannot be considered justified to begin early aggressive radiotherapy simply because examination of a lymph node has been reported to have disclosed chronic inflammation.

In recent years some hematologists have been developing the technic of lymph node aspiration in the diagnosis of lymphomas. It is quite probable, as experience in this technic is gained, that lymph node aspiration may occupy as important a place in the diagnosis of the various lymphomas as examination of the bone marrow now does in the diagnosis



UNIVERSITY OF MICHIGAN LIBRARIES

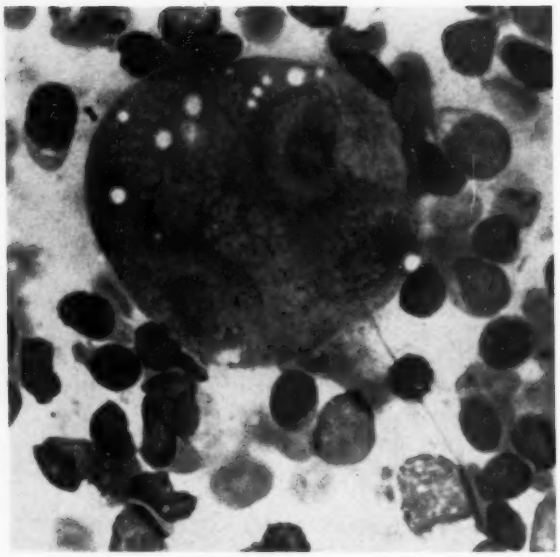


FIGURE 6. High-power photomicrograph of a Reed-Sternberg cell with the typical "mirror image" nuclei. The prominent nucleoli are easily seen. With Wright's or Giemsa's stain the nucleoli are deeply basophilic.

of other hematologic conditions. At present, lymph node aspiration alone probably should not be considered adequate for diagnosis, and surgical biopsy should always be performed. On the other hand, we have found it to be most helpful diagnostically in many situations. In those patients with several groups of enlarged nodes who have been reported by surgical biopsy as having a benign condition while the clinical picture suggests a progressive disease, lymph node aspiration can be performed with ease in many nodes and as frequently as desired with little pain or expense to the patient. When the picture has become suspicious, the lymph node is excised to establish the diagnosis. The procedure is as follows: The skin is sterilized in the usual fashion. Using a 20 cc. syringe and a 19 or 20 gauge needle, the lymph node to be aspirated is grasped firmly between the thumb and forefinger and the needle is thrust into the body of the lymph node. The use of procaine is not necessary and the procedure is usually less painful than the ordinary venipuncture. Suction is applied firmly in the same fashion as is done in a marrow aspiration. The needle is then withdrawn from the node and detached from the syringe. The syringe is filled with air to express the lymph node fluid from the needle onto a few cover slips. Smears are made in the usual fashion as is done for peripheral blood. These are quickly dried and stained with Wright's and Giemsa's stains.

### *Course and Prognosis*

As our knowledge of the natural course of lymphomas and leukemias has increased, our ideas about the prognosis have changed considerably. In addition, the results of even our present methods of therapy have not been adequately evaluated, although there have been many attempts to do so. In the first place, only in recent years have we begun to do lymph node biopsies at such an early date as is presently done. In the second place, it is almost impossible to establish the date of onset in these conditions, especially in the lymphomas and chronic lymphocytic leukemias. We have had numerous patients who had lymph node enlargement many years prior to the date of diagnosis but who did not go to a physician because the nodes were not troublesome or had regressed spontaneously.

In cases of leukemia the life expectancy can be anticipated somewhat more accurately than it can in cases of lymphoma.[3,6] Generally speaking, patients with acute leukemia rarely survive more than one or two years. Patients with monocytic leukemia have the poorest prognosis and most of them succumb within six months. Those with acute granulocytic leukemia fare only slightly better, half of the patients dying within four months; the rest of the patients usually survive about a year, although a patient rarely may survive for two or three years. The acute lymphocytic leukemias have the best prognosis of the acute disorders, and patients sometimes survive two or three years. These patients also respond best to chemotherapy and a number of remissions may be obtained. Patients with chronic granulocytic leukemia live from two to four years, but there are very few cases of chronic granulocytic leukemia that have been under "good control" and it is possible that this may be an important factor in their survival. Chronic lymphocytic leukemia has the best prognosis of all leukemias and the

span of life is extremely variable. A very large number of patients live 5 to 10 years. At the City of Hope Medical Center we have a number of patients who have lived 10 to 20 years with or without treatment. The probability is that the poor prognosis previously assigned to this disease was due to the fact that the patients did not consult a physician until they had well-advanced disease and that the period of survival was estimated from that time. We are beginning to recognize now that this disease begins insidiously and may remain relatively asymptomatic for 10 to 15 years.

The life span of patients with lymphoma is much more difficult to predict. Once again, earlier diagnosis has changed our entire concept of prognosis. Although in terms of statistical analyses it is generally stated that therapy does not prolong life, such studies are probably of little help in evaluating individual cases. We have all seen, for example, cases of Hodgkin's disease with mediastinal involvement and massive pleural effusion which without treatment would most surely lead to death from asphyxiation, but the simple administration of nitrogen mustard or irradiation of the mediastinum may completely alleviate this condition. We have all seen patients, too, who have come in with far-advanced disease, marked weight loss, fever and prostration and who have responded beautifully to nitrogen mustard; such patients most assuredly would succumb in a short period if it were not for these chemotherapeutic agents.

In general the prognosis of the lymphomas may be gauged by the maturity of the cell type. Thus, reticulum cell sarcoma usually has the poorest prognosis and most patients die within one or two years. Patients with lymphoblastic lymphosarcoma may fare somewhat better. Lymphocytic lymphosarcomas are more closely allied to chronic lymphocytic leukemia, and patients with lymphocytic lymphosarcoma seem to fare almost as well as patients with chronic lymphocytic leukemia. Giant follicular lymphoma was formerly thought to be a benign condition but is now recognized as a malignant lymphoma. However, it usually exists as a benign disorder for a long time, 10 to 20 years, until it finally advances into a more malignant phase, usually resembling lymphosarcoma.

Hodgkin's disease has an extremely variable prognosis and there are no reliable criteria for estimating survival.[7] It is generally held that women fare somewhat better than men.[8,9] Our own experience has borne this out. In any large series of cases it would appear that the extent of the disease at the time the patient is examined is the most accurate criterion for prognosis.[8] Thus the patient with generalized involvement may be expected to have a shorter life span than the patient with localized disease. However, there are innumerable exceptions to this, and many patients with extensive disease have survived 5 to 10 years with very little progression of the disease.

### *Treatment*

It is generally held that antibiotics and blood transfusion have done the most to enhance survival of patients with lymphomas or leukemias. It is probably a very common practice to administer vitamins to these patients. In leukemias it is doubtful that the vitamins benefit the patient in any way, and it is possible that in certain cases they may be harmful. At present, most of the chemotherapeutic agents for the leukemias are metabolic antagonists. Thus we have the folic acid antagonists, pyridoxine antagonists, and even riboflavin antagonists. Since we are trying to kill cells by preventing the utilization of vitamins, it would appear paradoxical that one should administer vitamins to such patients. In addition, although it is difficult to substantiate this, a few patients appear to have had an accelerated course of their disease or at least a sudden marked elevation of leukocyte count following the administration of large doses of vitamins. Suffice it to say, then, that it is probably unnecessary to administer vitamins to leukemic patients with the idea that they "can't do any harm."

Androgenic substances sometimes have been employed as adjunctive therapy in lymphomas.[10] Severe adverse effects associated with the administration of methyltestosterone in certain cases of lymphoma have recently been described, and in at least some of these

UNIVERSITY OF MICHIGAN LIBRARIES

cases the course of the disease appeared to be accelerated.[11] Methyltestosterone should be used with considerable caution in lymphomas.

The management of the lymphomas often presents the clearest therapeutic approach. For purposes of treatment the cases usually are divided into three general groups: (1) *localized*, confined to one group of nodes; (2) *regionalized*, disease process either all above or all below the diaphragm (neck, axillae and mediastinum without involvement of the liver or spleen); (3) *generalized*, hepatic or splenic enlargement with nodes in many areas involved.

Whenever feasible, radiotherapy is the treatment of choice, and we make one attempt to be aggressive in these cases. Based on the observation that lymphadenopathy does not recur, at least in Hodgkin's disease, if the patient has received over 3000 r to one site,[12,13] we attempt to deliver at least this amount to the involved sites in a "virgin" lymphoma. In such patients we are attempting curative therapy. If the disease is generalized, one of the chemotherapeutic agents is usually employed. However, there are many situations in which the patient may have generalized disease and yet radiotherapy may still be the treatment of choice. We recently had a patient with spinal Hodgkin's disease and a complete block in the midlumbar area resulting in hemiplegia. The patient had been treated with nitrogen mustard on several occasions, only to have his disease recur within months or weeks following administration of the drug. In this case the disease was so strategically located that only complete ablation of the tumor could prevent permanent paralysis. Such a patient should best have been given x-ray therapy to the spinal cord before the mustard. It is our general policy, then, when we see a patient for the first time and decide to embark on a course of radiotherapy, to be radical the first time and hope to destroy the tumor at its inception. At least we hope the tumor will not recur at the site treated, and it usually does not. In the previous decade, because it was known that lymphomas were very radiosensitive, small doses of x-ray were administered, usually amounts of 800 to 1000 r. Although good palliation was achieved, the nodes invariably recurred time and time again and the patient received many courses of x-ray, usually resulting in much higher doses of irradiation than he would receive by the technics we now use.

In the chemotherapy of lymphomas, nitrogen mustard, until recently at least, has been considered the treatment of choice. It is certainly a very helpful drug in these conditions and may result in repeated remissions. It is rare, however, to get a very long remission after the administration of nitrogen mustard. An occasional case may go on for several months or a year without recurrence, but most patients relapse within a few weeks or months.

Triethylene melamine (TEM) had a short-lived vogue in the management of lymphomas. The only advantage the drug appeared to have over nitrogen mustard was that it could be administered easily by mouth. However, its results are too unpredictable and in a number of cases its use has resulted in drastic depression of the bone marrow.

In the past few years a new mustardlike compound has been synthesized by the Chester-Beatty Institute in England. This compound is chlorambucil (LEUKERAN® or CB-1348). In our hands this drug has been at least as effective as nitrogen mustard, and perhaps surpasses it. It has some advantages over nitrogen mustard. It can be administered orally, does not produce nausea and vomiting as frequently, and appears to cause considerably less depression of bone marrow. There is some evidence, too, that this drug is more selective for neoplastic lymphoid tissue,[14] but this remains to be proved. It is supplied in 2 mg. tablets. Dosage ranges from 0.1 to 0.5 mg. per kilogram of body weight, an average being 0.2 per kilogram or 8 to 12 mg. a day. We have found that the dosage appears to depend on the tumor size rather than on the total body size, so that early in the treatment the patient may tolerate large dosages; as the tumor masses regress the dosage is rapidly decreased. A course of therapy consists of four to eight weeks of administration. However, we have used the drug as long as 6 to 18 months, continuing to obtain beneficial re-

sults.[14] In some cases it would appear that intermittent or maintenance therapy is desirable.

The adrenocortical steroids have been employed in the management of lymphomas with variable results. In some cases of reticulum cell sarcoma and lymphosarcoma even small doses of the steroids produce excellent results. Occasionally a patient will have a remarkable regression of tumor masses. As a rule, however, steroid therapy is disappointing. It seems to be most useful in patients who have secondary anemia or hypersplenic syndromes, and it may be beneficial in some patients in whom severe cachexia and anorexia have developed. Except for the decreased retention of salt and water with prednisone and prednisolone, these drugs do not seem to have any great advantage over cortisone. There is a distinct hazard in employing these hormones in the management of the lymphomas, and we have had a number of patients in whom bacterial and fungal infections have developed following steroid therapy. This is not completely unexpected, since it is known that there is an alteration of the immune mechanisms in certain lymphomas.[8,15]

When all other standard treatments have failed to induce palliation, phenylbutazone (BUTAZOLIDIN®) has been helpful in certain cases of Hodgkin's disease.[16] This drug is particularly useful in cases in which there are such systemic symptoms as fever, generalized aching, anorexia, sweating and weight loss. If a patient is to benefit from phenylbutazone, this benefit usually is seen within the first 24 or 48 hours. Generally there is an increase in sense of well-being, a return of appetite, a decrease in sweating and fever, and a disappearance of aches and pains. In some cases there may be a reduction in lymph node masses. If the drug is discontinued, symptoms usually recur within a few days. The drug is administered in larger doses for the first few days, 600 mg. being given in divided doses over a 24 hour period. As soon as improvement is noted, the dosage is reduced rapidly and the patient is maintained on 200 to 400 mg. a day. Although we have not yet observed the development of aplastic anemia in any such case (in fact the anemia frequently improves), the patients should be followed regularly with blood counts to avoid this hazard. By judicious use of phenylbutazone, improvement may be obtained for many months in some cases.

Except in the rare case of gastrointestinal lymphoma in which operation is performed because some other neoplasm is suspected, it is doubtful that surgery plays any role in management of lymphomas. Irradiation remains the treatment of choice in the localized cases, and in spite of the sporadic reports of so-called cures following radical dissection of nodes the surgical approach should be avoided.

Treatment of leukemias, at least the acute leukemias, is a more complex problem. Treatment of *acute granulocytic* and *acute monocytic* leukemia is at best discouraging. The most useful agents are antibiotics and fresh whole blood drawn in silicone-treated bottles. Folic acid antagonists probably have a limited place in management of acute leukemias in adults. 6-Mercaptopurine has produced a remission in only a small number of cases and sometimes aggravates the existing thrombopenia. It is not always necessary to use maintenance doses, although we have observed longer remissions with continuous therapy. The drug acts rather slowly, and usually two to eight weeks of administration are necessary to produce a remission.

Adrenocortical hormones are frequently employed in acute monocytic and granulocytic leukemia, but the results are equivocal. In patients with marked thrombopenia the steroids often help to control bleeding. They also rapidly alleviate acute toxic symptoms and produce a sense of well-being and an increase in appetite. However, in our experience they have not been helpful in inducing true hematologic remissions and we tend to employ the hormones for only a short time.

*Acute lymphocytic leukemia* is more responsive to therapy. 6-Mercaptopurine and adrenocortical steroids are both very helpful in treatment of this condition. For the most part we attempt to induce a remission with the adrenal hormones. In some cases very small doses of cortisone or prednisolone will produce striking benefit in a short time, mani-

UNIVERSITY OF MICHIGAN LIBRARIES

fested by alleviation of toxic symptoms, fall in temperature, increase in appetite, and decrease in bleeding tendencies. Over a period of a few weeks the anemia may improve and the immature cells may disappear from the blood and bone marrow. We are at present carrying out an extensive and carefully controlled study of massive steroid therapy versus conventional doses in acute leukemias. In cases that are resistant to small doses of cortisone, massive doses of cortisone or prednisolone, as much as 1 to 5 gm. a day, may produce prompt beneficial effects. We have had several patients in whom this has occurred. Daily determinations of the excretion of uric acid in the urine are helpful in evaluating response to steroid therapy.[17] If the drug is to be effective, the uric acid excretion will increase two to four times the basal level within the first few days of therapy. Once a remission is obtained, maintenance therapy is usually necessary or a relapse will occur within a few days or weeks.

Many other hematologists prefer to begin therapy with 6-mercaptopurine. The usual dosage is 2.5 mg. per kilogram of body weight per day by mouth, but some hematologists use as much as 6 mg. per kilogram. A complete hematologic remission may be expected in about 50 per cent of the patients with acute lymphocytic leukemia. Such remissions may last several months.

The folic acid antagonists have been helpful in a smaller group of cases. Two forms of the drugs are commonly employed, namely, AMINOPTERIN® and amethopterin (METHOTREXATE®). The daily dose ranges from 2.5 to 10 mg. Once a remission is achieved, usually in three to eight weeks, the drug may be continued or it may be stopped. If the drug is discontinued the bone marrow should be examined every two to four weeks, and at the first sign of relapse therapy should be instituted again. All the cytotoxic agents can be dangerous, and periodic examination of the bone marrow must be done to avoid irreversible depression.

The *chronic leukemias* are now more easily controlled than they were in previous years. Several agents are available. *Chronic granulocytic leukemia* is probably best treated with MYLERAN®, another alkylating agent. Four to 6 mg. of the drug is administered daily by the oral route, preferably before breakfast. Beneficial effects usually are not observed before 10 to 14 days, and may not be observed for three to four weeks. In some cases maintenance therapy appears to be necessary while in others it is not. Remissions may last from six months to over a year, and then second and third remissions may be induced. X-ray therapy over the spleen is still a helpful procedure in some cases, but use of Myleran is a cheaper and simpler method of therapy.

Another drug is available for the treatment of chronic granulocytic leukemia. This drug is derived from colchicine and is known as demecolcine or COLCEMIDE®.[18] It appears to be a much more effective inhibitor of cell mitosis than colchicine itself and apparently is one-thirtieth as toxic. It may be administered orally or intravenously. If the drug is given intravenously the results are rapidly seen within a few days to a week. If it is administered orally the response takes somewhat longer, usually two to three weeks. Dosage varies from 3 to 10 mg. a day, higher dosage levels sometimes being necessary. Once a remission is obtained, maintenance therapy must be continued in smaller doses or a relapse will occur within a few days. The drug is generally well tolerated. Nausea and anorexia may occur but usually subside after the drug has been administered for a week or more. Alopecia has occurred in a number of cases. Severe aphthous stomatitis may occur if excessive doses are given.

Management of *chronic lymphocytic leukemia* depends more on the time of treatment than on the type. Most patients tolerate the disease very well and do not require therapy for many months or years. If the leukocyte count is below 100,000 and the patient is asymptomatic, it is wisest to do nothing. Once symptoms appear, moderate anemia develops, or the white blood cell count rises to 100,000 or more, or if the lymph nodes and spleen have become so large as to be troublesome, treatment may be instituted.

The choice of therapy for chronic lymphocytic leukemia at present is between x-ray

and chlorambucil. X-ray therapy may be administered in two ways. Spray irradiation is very effective but has the handicap of requiring a room large enough to allow the patient to be completely bathed with roentgen rays. If this type of x-ray therapy is not feasible, radioactive phosphorus ($P^{32}$) may produce the same effect. Chlorambucil has been of particular value in chronic lymphocytic leukemia and would appear to be the chemotherapeutic agent of choice at present. Its action is more predictable than that of triethylene melamine or nitrogen mustard and it is less toxic than either of these drugs.

If anemia is a prominent manifestation of the disease, small doses of adrenocortical steroids are very helpful, especially if the patient has evidence of a hemolytic disease, with or without a positive Coombs test. Usually, prolonged maintenance therapy is required, although some patients do well if the drug is discontinued after several months. Recent studies in our laboratories have demonstrated the occurrence of hypogammaglobulinemia or agammaglobulinemia in some cases of chronic lymphocytic leukemia. These patients are more susceptible to infections, and strict attention must be paid to the selection of antibiotics to be used when treating them. Generally speaking, the bactericidal agents such as penicillin and streptomycin should be used in large doses rather than the broad-spectrum drugs, which usually are only bacteriostatic.

### *Conclusion*

I do not wish to make the classic medical cliché that "we have made great progress" in the lymphomas and leukemias, but I think it can modestly be stated that some forward strides have been made. A better understanding of the disease processes has suggested newer approaches to research. Only a decade or so ago the major therapeutic agent available was x-ray. Now there are several useful agents. As newer chemotherapeutic drugs are developed, it seems plausible that we shall be able to induce repeated remissions in cases even though they have become resistant to the previously used drugs. Until the ultimate cure is achieved, this may well be the more immediate hope. It is our experience that carefully planned therapy which is persistently pursued may result in prolonged survival. In many situations this means withholding treatment until the time is appropriate to administer it.

### REFERENCES


1. Sternberg, C.: Zur Kenntnis des Chloroms (Chloromyelosarkon). Beitr. path. Anat. 37:437, 1905.
2. Isaacs, R.: Lymphosarcoma cell leukemia. Ann. Int. Med. 11:657 (October) 1937.
3. Rosenthal, N.: Lymphomas and leukemias. Bull. New York Acad. Med. 30:583 (August) 1954.
4. Ludman, H. and Spear, P. W.: Reed-Sternberg cells in the peripheral blood; report of case of Hodgkin's disease. Blood 12:189 (February) 1957.
5. Varadi, S.: Hodgkin's disease: Specific findings in sternal puncture material. Brit. J. Haemat. 1:184 (April) 1955.
6. Wintrobe, M.: Clinical Hematology. Ed. 4. Philadelphia, Lea & Febiger, 1956, p. 951.
7. Finkbeinder, J. A., Craver, L. F. and Diamond, H. D.: Prognostic signs in Hodgkin's disease. J.A.M.A. 156:472 (October 2) 1954.
8. Hoster, H. A., Dratman, M. B., Craver, L. F. and Rolnick, H. A.: Hodgkin's disease, 1832-1947. Cancer Res. 8:49 (February) 1948.
9. Shimkin, M. B., Oppermann, K. C., Bostick, W. L. and Low-Beer, B. V. A.: Hodgkin's disease: Analysis of frequency, distribution and mortality at the University of California Hospital, 1914-1951. Ann. Int. Med. 42:136 (January) 1955.
10. Craver, L. F.: Recent advances in treatment of inoperable cancer. Bull. New York Acad. Med. 28:385 (June) 1952.
11. Shanbrom, E. and Finch, S. C.: Adverse effects of methyltestosterone administration in lymphomas. Cancer 10:964, 1957.
12. Craver, L. F.: Lymphomas and leukemias: Value of early diagnosis and treatment. J.A.M.A. 136:244 (January 24) 1948.
13. Lenz, M., Wells, J. and Stout, A. P.: Hodgkin's disease and lymphosarcoma. In Portmann, U. V.: Clinical Therapeutic Radiology. New York, Thomas Nelson & Sons, 1950, p. 545.
14. Shanbrom, E.: Chlorambucil treatment of reticuloendothelial neoplasias; review of 140 cases, with a note on large dosage and continuous administration. American Society of Hematology, April 1958.
15. Schier, W. W., Roth, A., Ostroff, G. and Schrift, M. H.: Hodgkin's disease and immunity. Am. J. Med. 20:94 (January) 1956.
16. Rottino, A., Joffe, A. and Hoffmann, G.: Phenylbutazone (Butazolidin), a useful chemotherapeutic agent for Hodgkin's disease. A.M.A. Arch. Int. Med. 93:561 (April) 1954.
17. Shanbrom, E.: Uric acid excretion as a guide to steroid therapy of acute leukemia. Clin. Res. Proc. 6:77, 1958.
18. Moeschlin, S., Meyer, H. and Lichtman, A.: Ein neues Colchicum-nebenalkaloid (Demecolcin Ciba) als Cytostaticum myeloischer Leukämien. Schweiz. med. Wchnschr. 83:990, 1953.




UNIVERSITY OF MICHIGAN LIBRARIES

# Diuretics in the Treatment of Hypertension

HARRIET P. DUSTAN*

*The Cleveland Clinic Foundation, Cleveland*

*The orally effective diuretic agent chlorothiazide has greatly simplified the treatment of hypertension and has reawakened interest in the role of sodium and water in the mechanism of this condition.*

*Chlorothiazide lowers arterial pressure and enhances the effectiveness of ganglion-blocking agents given either singly or in combination.*

*From studies conducted by the author, it was concluded that the decrease in the volume of plasma caused by short-term administration of chlorothiazide decreases cardiac output and increases vasomotor tone, thereby producing a situation in which antihypertensive drugs which act on the central nervous system become more effective.*

HARRIET P. DUSTAN

During the past eight years an extraordinary advance has occurred in the treatment of hypertension. In this brief period, four groups of antihypertensive drugs have been developed which have changed radically the outlook for hypertensive patients. Prior to this, treatment was far from satisfactory. Low sodium diets were effective in some patients, but only a few could or would follow regimens rigidly enough to secure a therapeutic response. Sympathectomy, successful in many patients with mild hypertension, was not recommended for those who were azotemic or who had other signs of advanced arteriolar disease and urgently needed good therapy. Since 1950, however, the situation has changed greatly. At that time, hydralazine and the ganglion-blocking agent hexamethonium were released for trial; both proved to have long-term effectiveness in numerous hypertensive patients. Other ganglionoplegic drugs were developed which were more effective than hexamethonium. Then followed the development of reserpine, a centrally acting vasodepressor

*Research Division, The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

Presented before the forty-third annual Assembly of the Interstate Postgraduate Medical Association at Cleveland.

which proved to be antihypertensive when used alone in some patients; in other patients, it allowed a reduction in the therapeutic level of ganglion-blocking drugs or mitigated their side effects.

Although not all hypertensive patients responded to the available drugs, the older treatments received much less emphasis. Sympathectomy came to be recommended for the patients who could not or would not take antihypertensive drugs; low sodium diets were prescribed only when congestive cardiac failure had supervened. The drug most recently introduced[1] is the orally effective diuretic agent chlorothiazide. Not only has it simplified greatly the treatment of many hypertensive patients, but its effectiveness also has reawakened interest in the role of sodium and water in the mechanism of hypertension. The antihypertensive effects of chlorothiazide are not well understood. In part, they seem to depend on its powerful diuretic and saluretic properties, but the possibility of an intrinsic antihypertensive action also must be considered. The purpose of this report is to review the early clinical experience with chlorothiazide and to describe a possible mechanism of action.

### *Clinical Experience With Chlorothiazide*

In late 1957 and early 1958, the first reports[2-10] of the effectiveness of chlorothiazide in the treatment of hypertension were published. These summarized experience with this drug in 181 patients. Of the 37 who received chlorothiazide alone, 19 responded favorably; 15 normotensive patients who were treated experienced no change in arterial pressure. In 128 patients, chlorothiazide was added to various antihypertensive regimens, and control of blood pressure improved in 114. Sixteen patients who had previously undergone sympathectomies obtained significant reduction of blood pressure when treated with this diuretic. These reports emphasized that chlorothiazide enhanced the effectiveness of ganglion-blocking drugs and pointed out the responsiveness of patients who had been unsuccessfully or inadequately treated by sympathectomy.

Our experience[11] has been similar to that reported. We gave chlorothiazide to 40 hypertensive patients who were receiving other antihypertensive agents, singly or in combination. Twenty-three patients were taking ganglionoplegic drugs, with or without adjunctive reserpine or hydralazine; with the addition of the diuretic, better control of blood pressure was achieved in 19. When chlorothiazide was given to 17 patients receiving hydralazine or reserpine or both, further reduction of blood pressure occurred in nine.

These antihypertensive effects do not seem to be peculiar to chlorothiazide and similar diuretics, since mercurial diuretics can lower arterial pressure[12] and can enhance effectiveness of ganglion-blocking drugs.[11]

Continued experience with chlorothiazide and with the more recently introduced dihydrochlorothiazide has confirmed the early observations that diuretic therapy not only simplifies the treatment of hypertension but also increases the patient's sense of well-being. However, these drugs are not without serious side effects; the most important of these is hypokalemia, resulting from increased excretion of potassium. Hypokalemia is always potentially serious, particularly in patients receiving digitalis. Wilkins[9] has stressed this danger and has advocated use of low dosages of chlorothiazide for maintenance therapy. He suggests an initial dosage of 125 mg. three times daily, which is to be increased to 250 mg. three times daily if the lower dose is ineffective. To guard against hypokalemia, we have employed an interrupted dosage schedule and have used 500 to 1000 mg. twice a day for three to five consecutive days each week. The advantage in this regimen is that potassium can be repleted during the drug-free days; there also is a disadvantage, in that sodium is retained and large weight gains, which are uncomfortable but not dangerous, can occur.

### *Possible Mechanism of Action*

Since chlorothiazide increases the urinary excretion of sodium, chloride and water, it causes a negative balance of sodium and water and a shrinkage of the volume of plasma and extracellular fluid. Mercurial diuretics and low



UNIVERSITY OF MICHIGAN LIBRARIES

sodium diets produce similar effects. Accordingly, it seems likely that some of the antihypertensive effects of diets and diuretics are related to augmented excretion of sodium, to decreases in the volume of plasma and extracellular fluid, or to both features.

To explore the relationships among excretion of sodium, changes in the volume of plasma and the requirement of ganglion-blocking drugs, and blood pressure in hypertensive patients, we studied the sequential changes in these functions produced by administration of chlorothiazide over a period of several days.[10] This study included nine hospitalized patients who had previously taken ganglionoplegic agents for months or years. Five, who had followed low sodium diets, were continued on these regimens during the entire period of observation; unrestricted sodium intake was allowed in three patients, and one received a low sodium diet during the days that chlorothiazide was given. The study was divided into three periods: control, diuretic and postdiuretic. During the diuretic period, the patients were given 1 gm. chlorothiazide twice daily for three to four days; during the postdiuretic period they received no diuretic, but were given supplemental sodium in amounts equal to one-half or all that was lost in the urine during the diuretic period. Functions measured included blood pressure (lying and standing) four times per day, daily requirements of ganglion-blocking drugs, and 24 hour excretions of water and sodium. The volume of plasma was measured at the end of each study period.

During the administration of chlorothiazide, the excretion of sodium and water increased and all patients lost weight; the volume of plasma diminished and hematocrit rose. The requirement of ganglion-blocking drugs decreased sharply; despite this, supine arterial pressure was lower in most patients and orthostatic hypotension was exaggerated in all. When the diuretic was stopped and repletion of sodium was carried out, weight gains and positive sodium and water balance occurred in all patients. Arterial pressure, the requirement of ganglion-blocking drugs, volume of plasma, and hematocrit all tended to return to control values. The results of this study showed that the negative balances of sodium and water induced by chlorothiazide in hypertensive patients are in some way related to enhancement of the effectiveness of ganglionoplegic drugs, but there was no differentiation between the roles played by depletion of sodium and by shrinkage of the volume of plasma.

Chlorothiazide enhances the orthostatic hypotension of ganglion-blocking drugs; thus, it also might decrease cardiac output. Accordingly, we studied the hemodynamic effects of chlorothiazide in nine hypertensive patients who were not receiving any other antihypertensive drugs.[13] Cardiac output was measured by the dye dilution technic. Four to eight days of treatment with chlorothiazide decreased cardiac output and the volume of plasma in all patients. Arterial pressure was somewhat decreased; however, it was disproportionately less than the decrease in cardiac output, so that total peripheral resistance was elevated. To test whether or not the decrease in plasma volume was the cause of the decrease in cardiac output, one patient was given 500 ml. salt-free dextran; this infusion resulted in a prompt return of the output to the prechlorothiazide levels and a decrease in total peripheral resistance.

In another part of this investigation, we found that chlorothiazide also greatly increased the hypotensive effects of tetraethylammonium chloride given intravenously and that this ganglion-blocking drug could lessen the increase in total peripheral resistance that resulted from the diuretic-induced oligemia. From these studies, we concluded that the decrease in the volume of plasma, caused by the short-term administration of chlorothiazide, not only decreases cardiac output but also increases vasomotor tone, thereby producing a situation in which antihypertensive drugs which act on the central nervous system become more effective in lowering arterial pressure. The studies described dealt only with the early effects of treatment with chlorothiazide. It seems likely that during prolonged treatment the mechanism of action may change so that marked hypovolemia and decreases in cardiac output are lessened.

## REFERENCES

1. Novello, F. C. and Sprague, J. N.: Benzothiadiazine dioxides as novel diuretics. J. Am. Chem. Soc. 79:2028 (February) 1957.
2. Freis, E. D. and Wilson, I. M.: Potentiating effect of chlorothiazide (Diuril) in combination with antihypertensive agents: Preliminary report. M. Ann. District of Columbia 26:468, 516 (September) 1957.
3. Freis, E. D., Wanko, A., Wilson, I. M. and Parrish, A. E.: Treatment of essential hypertension with chlorothiazide (Diuril). J.A.M.A. 166:137-140 (January 11) 1958.
4. ——: Chlorothiazide in hypertensive and normotensive patients. Ann. New York Acad. Sc. 71:450-455 (February 3) 1958.
5. Heider, C., Dennis, E. and Moyer, J. H.: Chlorothiazide potentiation of ganglionic blockade in patients with hypertension. *Ibid.*, pp. 456-464.
6. Hollander, W. and Wilkins, R. W.: Chlorothiazide: A new type of drug for the treatment of arterial hypertension. Boston M. Quart. 8:69-75 (September) 1957.
7. Wilkins, R. W., Hollander, W. and Chobanian, A. V.: Chlorothiazide in hypertension: Studies on its mode of action. *Ibid.*,[4] pp. 465-472.
8. Wilkins, R. W.: New drugs for hypertension with special reference to chlorothiazide. New England J. Med. 257:1026-1030 (November) 1957.
9. ——: Precautions in use of antihypertensive drugs, including chlorothiazide. J.A.M.A. 167:801-807 (June) 1958.
10. Tapia, F. A., Dustan, H. P., Schneckloth, R. E., Corcoran, A. C. and Page, I. H.: Enhanced effectiveness of ganglion-blocking agents in hypertensive patients during administration of a saluretic agent (chlorothiazide). Preliminary communication. Lancet 2:831-833 (October) 1957.
11. Dustan, H. P.: Chlorothiazide in the treatment of hypertension. Seminar Report. Philadelphia, Merck Sharp and Dohme, division of Merck & Co., Inc., Winter 1958.
12. Hollander, W. and Chobanian, A. V.: The mode of action of chlorothiazide and mercurial diuretics as an antihypertensive agent. J. Clin. Invest. 37:902 (June) 1958.
13. Dustan, H. P., Cummings, G. R., Corcoran, A. C. and Page, I. H.: A mechanism of chlorothiazide, enhanced effectiveness of hypertensive ganglionoplegic drugs. Circulation 19:360-365 (March) 1959.


# MEETINGS and Postgraduate Courses

American College of Allergists, Miami Beach: Graduate instructional course and annual congress, February 28-March 4, at The Americana Hotel, Bal Harbour. For further information, write to: Dr. John D. Gillaspie, Treasurer, 2049 Broadway, Boulder, Colorado.

American Nuclear Society, Washington, D. C.: Winter meeting, November 4-6, at the Sheraton Park Hotel. For further information, write to: Corbin Allardice, Chairman of the Publicity Committee, 1818 H Street, N. W., Washington 25, D. C.

Association of Military Surgeons, Washington, D. C.: Annual convention, November 9-11, at the Mayflower Hotel. For further information, write to: Association Headquarters, 1726 Eye Street, N. W., Washington 6, D. C.

Columbia University Faculty of Medicine, New York: Postgraduate courses in clinical medicine, October 1959-June 1960: dermatology, internal medicine, neurology, ophthalmology, orthopedic surgery, otolaryngology, pathology, physical medicine and rehabilitation, physiology, psychiatry, public health, radiology, surgery and urology. For further information, write to: Dean of the Faculty of Medicine, 630 West 168th Street, New York 32.

New York University Post-Graduate Medical School, New York: Postgraduate course in neuro-ophthalmology, January 18-22. For further information, write to: Office of the Associate Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16.

University of Pennsylvania Graduate School of Medicine, Philadelphia: Conference on medical education as related to residency training programs, December 3-4. For further information, write to: Dr. George B. Koelle, Dean, University of Pennsylvania Graduate School of Medicine, Philadelphia 4.

University of Texas M. D. Anderson Hospital and Tumor Institute, Houston: Clinical conference on tumors of the head and neck, November 13-14, presented in cooperation with the University of Texas Postgraduate School of Medicine. For further information, write to: Editorial Office, M. D. Anderson Hospital, Houston 25.

University of Utah College of Medicine, Salt Lake City: Postgraduate refresher course in anesthesiology, February 8-11. For further information, write to: Dr. C. Hilmon Castle, Director, Division of Graduate and Postgraduate Medical Education, 116 Medical Building, Salt Lake City.



UNIVERSITY OF MICHIGAN LIBRARIES

*The four major types of urinary fistulas are renal, ureteral, vesical and urethral. Urinary fistulas may be congenital or acquired. Symptoms depend on the type and site of the fistula. Diagnosis includes recognition of the fistula and determination of its cause. Treatment may require cooperation of the urologist, general surgeon and internist.*

# Urinary Fistulas

CHESTER C. WINTER, RODERICK D. TURNER AND WILLARD E. GOODWIN*

*University of California Medical Center, Los Angeles*

FISTULAS involving the urinary tract are an ancient medical problem, and the literature contains numerous reports dealing with the etiology, symptoms and new or improved methods of treatment. These fistulas always have been considered one of the most difficult problems in medicine, and their treatment continues to test the ingenuity of the surgeon. It is our purpose to review the etiology, symptoms, diagnosis and management of urinary fistulas, and to describe our experience with these lesions.

CHESTER C. WINTER

RODERICK D. TURNER

WILLARD E. GOODWIN

### *Classification*

On an anatomic basis, urinary fistulas may be divided into four major types, namely, renal, ureteral, vesical and urethral. Each of these major types may be subdivided according to the extra-urinary organ with which the fistula communicates (table 1).

### *Etiology*

Urinary fistulas may be congenital or acquired. Acquired fistulas may be caused by inflammation, operative trauma, neoplasms or foreign bodies. Table 1 shows the causes of 48 urinary fistulas which were observed in a group of 37 cases. The incidence of the various causes depends on the site of the fistula, the sex and age of the patient, and the type of practice or hospital.

*Nephro-intestinal fistulas* most frequently

*Department of Surgery, Division of Urology, University of California Medical Center and Wadsworth Veterans Administration Center, Los Angeles, and the Harbor General Hospital, Torrance, California.

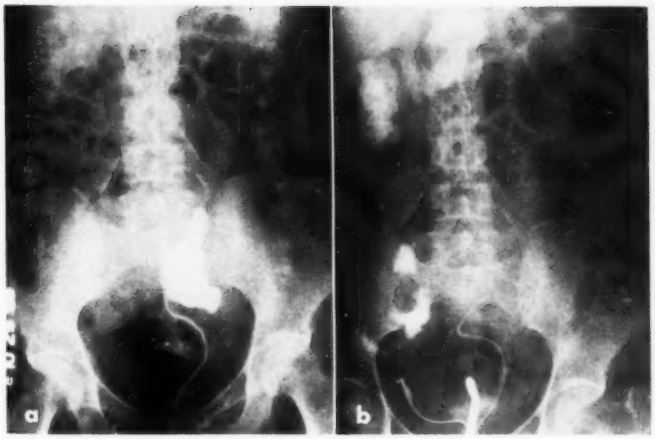


FIGURE 1a. Left retrograde pyelogram showing hydronephrotic pelvic kidney; b. right retrograde pyelogram showing pelvic kidney communicating with the small bowel.

are due to obstruction of the urinary tract caused by pyelonephritis or trauma. Neoplasm has never been reported as a cause of this type of fistula. We have been fortunate in being able to observe the case of nephrocolonic fistula reported by Ellik and Getz[1] in 1953. The patient was a 62 year old white woman who had a left perinephric abscess, multiple renal calculi, and a poorly functioning kidney. Retrograde pyelography disclosed a communication between the left kidney and the descending colon. The perinephric abscess was drained, and the left kidney was removed one month later. The opening in the bowel could not be visualized during the operation, but it subsequently closed spontaneously. The sequence of events in this case apparently was as follows: (1) obstruction of the ureter by a calculus, (2) infected hydronephrosis, (3) rupture of the kidney, (4) perinephric abscess, and (5) a fistula between the kidney and the colon.

TABLE 1

CLASSIFICATION OF URINARY FISTULAS

| TYPE | NUMBER |
|---|---|
| Renal | 2 |
| Nephrogastric | |
| Nephro-enteric | |
| Inflammatory | 1 |
| Nephrocolonic | |
| Inflammatory | 1 |
| Nephroperitoneal | |
| Nephrocutaneous | |
| Ureteral | 4 |
| Uretero-enteric | |
| Ureterocolonic | |
| Postoperative | 1 |
| Uretero-appendiceal | |
| Ureterorectal | |
| Postoperative | 1 |
| Ureteroperitoneal | |
| Postoperative | 1 |
| Ureterovaginal | |
| Postoperative | 1 |
| Ureterocutaneous | |
| Vesical | 30 |
| Vesico-enteric | |
| Inflammatory | 2 |
| Vesicocolonic | |
| Inflammatory | 4 |
| Neoplastic | 5 |
| Postoperative | 2 |
| Vesico-appendiceal | |
| Vesicorectal | |
| Postoperative | 9 |
| Vesicoperitoneal | |
| Vesicovaginal | |
| Postoperative | 3 |
| Neoplastic | 1 |
| Vesicocutaneous | |
| Postoperative | 4 |
| Urethral | 12 |
| Urethrorectal | |
| Postoperative | 7 |
| Foreign body | 1 |
| Congenital | 1 |
| Urethrovaginal | |
| Urethrocutaneous | |
| Postoperative | 2 |
| Foreign body | 1 |
| TOTAL | 48* |

*These 48 fistulas were observed in a group of 37 cases.

The presence of a nephro-ileal fistula also was demonstrated by retrograde pyelography in another case. The patient was a 40 year old white woman who had severely infected, hydronephrotic, pelvic kidneys (figure 1a and b). Ten years previously, a calculus had been removed from the right kidney with difficulty. Treatment of the fistula consisted of right nephrectomy and excision of the involved segment of the ileum.

*Uretero-intestinal fistulas* also are most frequently associated with inflammatory disease or trauma. A 45 year old white man was in the hospital for treatment of a calculus of the left ureter. The calculus was removed surgically at the third attempt, and a ureterocolonic fistula developed postoperatively. The fistula ulti-

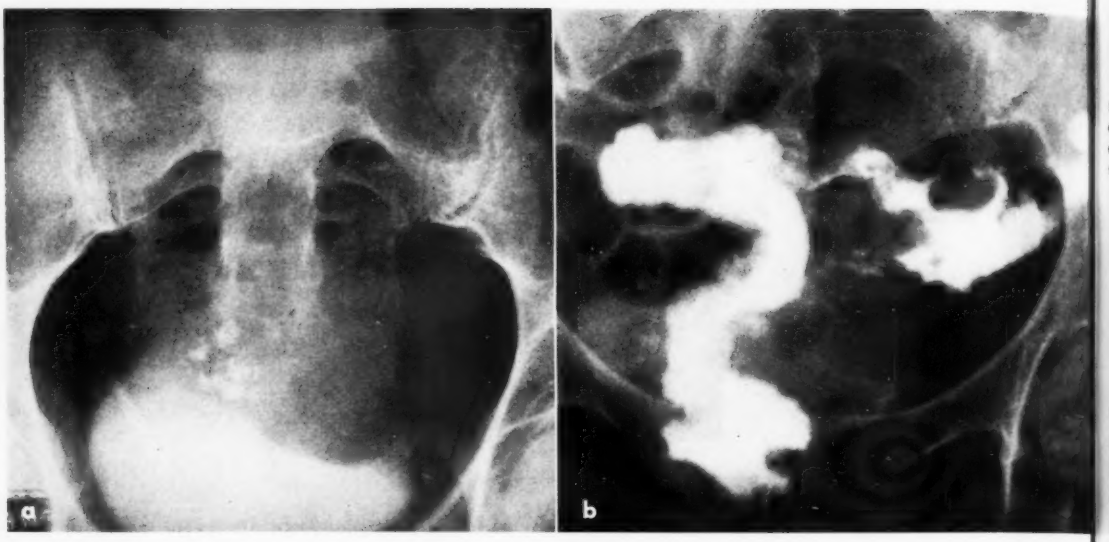


FIGURE 2a. Cystogram showing a mass impinging on the left side of the upper portion of the bladder; b. contrast medium in the sigmoid colon outlines diverticula, a fistulous tract and a filling defect.

mately healed spontaneously after prolonged drainage, but a mild stricture of the ureter remained.

*Vesico-intestinal fistulas*[2-4] are most commonly due to inflammatory disease. The next most frequent causes are neoplasms, surgical trauma and congenital defects, which usually include an imperforate anus. Diverticulitis of the colon is the most frequent inflammatory cause. The next most frequent cause of this type is regional enteritis. The following case reports illustrate the variety and complexity of vesico-intestinal fistulas.

*Case 1*—A 57 year old white woman was seen because of anorexia, loss of weight, dysuria, frequency of micturition, fecaluria, chills, fever, and blood in the stools. A mass was palpable in the left lower quadrant of the abdomen. Cystography revealed a mass impinging on the left side of the upper portion of the bladder (figure 2a). Roentgenographic examination with a contrast medium disclosed a filling defect in the sigmoid colon, diverticula, and a fistula which communicated with the bladder (figure 2b). A diagnosis of diverticulitis was made, and a transverse colostomy was performed. The left ureter, which had been compressed by the mass, returned to normal and the mass seemed to shrink. However, the urinary symptoms persisted, and an exploratory laparotomy was performed. The mass involving the sigmoid colon and the bladder was removed, and the bladder and the sigmoid colon were closed primarily. The mass was found to be a carcinoma, and the patient died subsequently.

*Case 2*—A 43 year old Mexican man was admitted to the hospital because of pneumaturia, fecaluria, anorexia, loss of weight, pain in the lower part of the abdomen and urinary infection. The symptoms had been present for one month. Roentgenographic examination with an opaque enema disclosed a deformity of the colon, but no fistula. Colostomy and transurethral biopsy of the bladder were performed. The diagnosis was transitional cell carcinoma of the bladder and metastatic involvement of the liver. The patient died, and necropsy revealed that he also had an adenocarcinoma of the colon.

*Case 3*—A 47 year old white woman was seen in urologic consultation because of fecaluria, pneumaturia, and drainage of purulent material from an abdominal sinus tract and

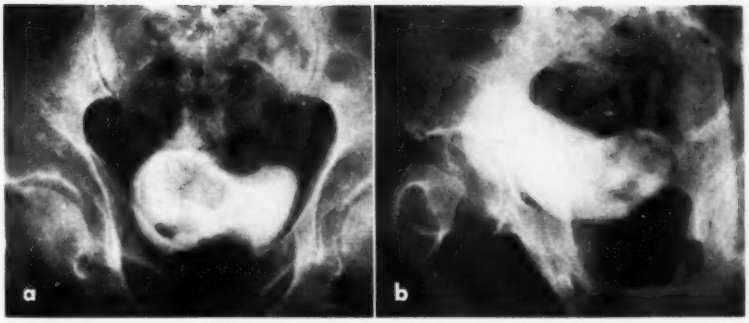



FIGURE 3a and b. Anterior and oblique cystograms showing an extrinsic filling defect of the left side of the dome of the bladder.

the vagina. Hysterectomy had been performed five years previously. A pelvic abscess had been drained subsequently, and an abdominocolonic fistula had developed. Several attempts to drain the abscess had resulted in the development of additional fistulas between the colon and the vagina and between the colon and the bladder. The cause of the disease was not established until biopsy of the bladder and the wall of a fistula disclosed the presence of carcinoma. Owing to the development of distressing symptoms, the urine was diverted to the skin by means of bilateral uretero-ileocutaneous anastomosis, and a colostomy was performed. The patient died subsequently of carcinomatosis.

*Case 4*—A 63 year old white man was known to have had diverticulitis of the colon and recurrent cystitis. He usually had responded to the administration of antibiotics, but a pelvic abscess had been drained on one occasion. A pelvic mass had developed gradually, and it had encroached on and drained into the bladder (figure 3a and b). After preoperative preparation of the bowel with antibiotics, the mass and the involved portions of the bowel and bladder were resected *en bloc*. The ureter was protected by the insertion of a catheter. The continuity of the sigmoid colon and bladder was re-established by a one stage procedure. The patient has had no further difficulty since the operation. We feel that this operative procedure is the ideal way to manage a lesion of this type.

*Case 5*—A patient who had had regional enteritis for 20 years was found to have multiple fistulas between the ileum, bladder and colon. They were manifested by fecaluria, dysuria, frequency of micturition, and loose stools. The urinary symptoms were relieved by ileostomy. Subsequently, the fistulous area and the diseased portion of the ileum were resected. After anastomosis of the ileum, he again passed feces in the urine. Cystography disclosed a vesicocolonic fistula, and a transverse colostomy was performed.

*Case 6*—A 32 year old white man had had regional ileitis for three years and cystitis and a necrotic ulcer for two years. During the month before he was admitted to the hospital, he had noted pneumaturia. Roentgenographic examination with a barium enema revealed the regional enteritis (figure 4a). A cystogram made after cystoscopic catheterization and the injection of opaque medium into an opening in the bladder wall disclosed a filling defect in the small bowel and a vesico-ileal fistula (figure 4b). Roentgenographic examination disclosed an extrinsic filling defect of the sigmoid colon (figure 4c). The fistula and the involved portions of the ileum and bladder were resected *en bloc*. A communication into the sigmoid colon was closed. Enterocolonic anastomosis was established primarily, and the bladder was closed.

*Vesicovaginal fistulas* most often are due to surgical or obstetric trauma. They may be due to neoplasms, or they may be congenital.

*Case 7*—A vesicovaginal fistula and a right uterovaginal fistula developed in a 33 year old white woman after a radical hysterectomy had been performed for carcinoma of the cervix.

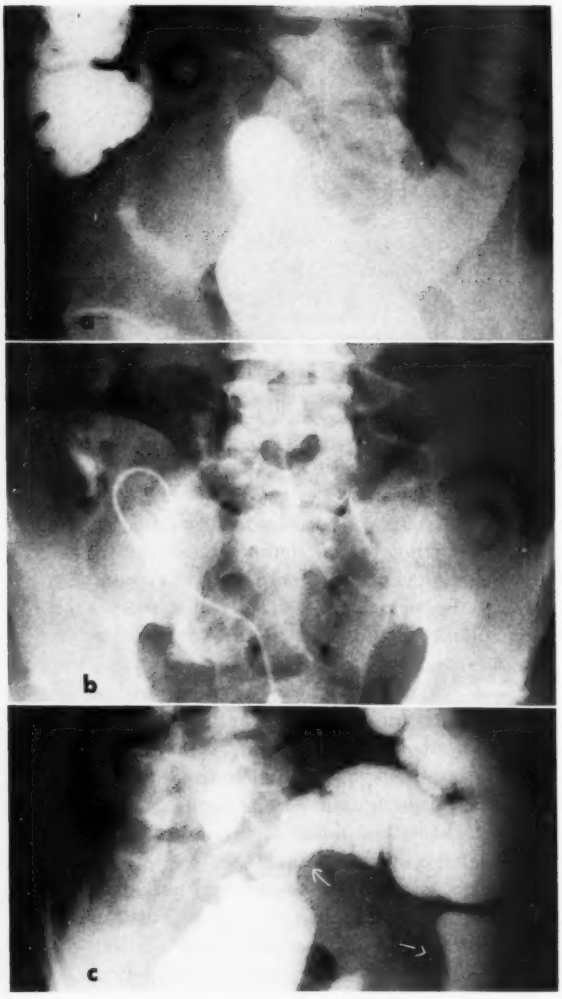



FIGURE 4a. Regional enteritis shown by roentgenogram made with a barium enema; b. cystogram showing opening in the bladder wall, a filling defect in the small bowel, and a vesico-ileal fistula; c, roentgenogram showing filling defect in the sigmoid colon.

Two attempts to close the fistulas as well as reimplantation of the ureter into the bladder were unsuccessful. A further attempt to close the fistulas will be made by using an isolated segment of ileum to replace the lower part of the right ureter.

*Vesicorectal fistulas* and *urethrorectal fistulas* usually are due to surgical trauma. Needle biopsy of the prostate gland prior to prostatic surgery occasionally may predispose to rectal injury at the time of the subsequent operation. A known previous injury of the rectum is a contraindication to radical retropubic prostatectomy in cases of carcinoma. Two of the fistulas in our series developed under these circumstances. However, radical perineal prostatectomy is safe if performed carefully.

### *Symptoms and Signs*

The symptoms depend on the type and site of the fistula. The passage of intestinal contents (fecaluria) or flatus (pneumaturia) in the urine is an indication of an intestinal communication. The type of intestinal contents may indicate the level of the communication, i.e., food from the stomach, succus entericus from the small bowel, and feces from the colon or rectum. Determination of the pH of the urine may be helpful since an alkaline fluid rarely would be gastric in origin, and an acid fluid would not come from the small bowel. Rapid or chronic loss of contents of the stomach or small bowel may cause electrolyte imbalance, loss of weight, avitaminosis and anemia. The initial symptom may be leakage of fluid from the skin or vagina or the passage of watery stools identifiable as urine. Chills, fever, dysuria, urinary frequency or urgency, tenderness and pain may occur as a result of infection and urinary obstruction. A palpable abscess or tumor may be a sign of an impending fistula (figure 5). Partial or complete intestinal obstruction may occur. The presenting symptoms initially may draw attention to either the genitourinary system or the gastrointestinal tract.

### *Diagnosis*

The diagnosis includes the recognition of the fistula and the determination of its cause. The history and physical examination may immediately clarify the situation. The presence of traumatic or congenital lesions may be suspected by their association with operation or childbirth, but inflammatory and neoplastic lesions usually offer a formidable problem in differential diagnosis. Careful digital examination and visual examination of the

rectum and vagina with appropriate instruments are required when urine is expelled from these organs. Sigmoidoscopy, vaginoscopy and urethroscopy frequently will help to localize the fistula. If the fistulous opening is identified in this manner, it may be catheterized, or opaque medium, dye or milk may be injected into it directly. Carmine or charcoal often will appear in the urine after it has been taken by mouth. Additional procedures include gastrointestinal, colonic, vesical and pyeloureteral roentgenograms made with contrast medium other than barium.

Aortography has been recommended as an aid in the study of nephrocolonic fistulas.[1] Finally, efforts should be made to perform a biopsy of the fistulous tract in order to establish the cause and to rule out the presence of carcinoma. Information gained in this way is invaluable in determining the prognosis and in planning the treatment.

### *Treatment*

When feasible, *en bloc* resection of the fistulous tract and involved portions of adjacent organs is the primary objective in most cases. This may necessitate temporary or permanent diversion of the feces or urine, or both, as part of the definitive or palliative therapy. Thus, a one to three stage plan may be necessary. The intestinal or urinary tract should be prepared adequately with antibiotics, but this type of treatment should be used judiciously. The use of antibiotics undoubtedly has reduced the morbidity and mortality in cases of fistula. Initially, inflammatory lesions usually are treated conservatively in the hope that they will close spontaneously. Adequate catheter drainage is indicated in cases of tiny vesical fistulas. In addition to the use of antibiotics, local care, dietary measures, nursing care, drainage of abscesses, and diversion of the feces and urine may precede the definitive surgical repair by a generous period of time. Another type of treatment available for fistulas which are accessible to the exterior is fulguration or cauterization of the epithelialized fistulous tract. The treatment of a urinary fistula may require the cooperative effort of the urologist, the general surgeon and the internist.

FIGURE 5. Serration of right side of dome of the bladder caused by an abscess and preceding a vesico-intestinal fistula.

Recently, there has been a trend toward initiating surgical repair at an early date. Burkholder[5] advocates the use of a rectal "pull-down" operation as soon as a postoperative vesicorectal or urethrorectal fistula is recognized, while Nourse[6] performs a primary transrectal repair immediately.

We have developed a technic for handling recto-urinary fistulas which occur after prostatectomy. This technic has been described in detail elsewhere,[7] but it will be summarized briefly here. The perineal structures are widely exposed, and the fistula is transected. Multiple layers are developed in both the urinary and rectal edges of the fistula. Both sides are then closed in two layers by arranging the suture lines at right angles. The rectum is mobilized downward and the bladder upward to avoid approximating the sutured areas, and the levator ani muscles are interposed. Adequate postoperative drainage of the urine is maintained by the use of suprapubic and urethral catheters. Appropriate use of antibiotics before and after operation, proper preparation of the bowel, and careful diagnostic studies are essential for the success of this method. In nine cases in which this method was used, the healing occurred by first intention. We

believe that this operation may be carried out within six to eight weeks after the injury.

If a rectal laceration is recognized during a perineal operation on the prostate and before the urinary tract has been opened, the rectum should be repaired as described previously, and the perineal operation should be abandoned. Prostatic biopsy may be accomplished without opening the urinary tract, if this is the purpose of the operative procedure. Opening of the urinary tract entails too great a risk of the development of a fistula, and the penalty to the patient and the surgeon does not seem justified. It would seem proper, however, to change to a retropubic approach and to proceed with enucleation of the prostate if the posterior capsule of the gland has not been violated from below. On the other hand, if rectal injury is discovered after the urinary tract has been opened, the surgeon might as well complete the planned operation. Closure should be made carefully by using the multiple technic which has just been described.

Today, ureteral fistulas no longer are an absolute indication for nephro-ureterectomy. The gap left by ureterectomy may be bridged very easily with an isolated segment of ileum.[4] Also, the vesical capacity which has been decreased by fistulous disease may be enlarged by the use of isolated segments of the ileum or sigmoid colon. Collins and Jones[8] recently have advocated the use of cortisone in cases of postoperative fistula in order to soften the fibrous reaction and thus permit earlier repair.

Nephrocolonic fistulas are best handled by nephrectomy if the contralateral kidney is functioning well. Otherwise, an attempt should be made to repair the involved kidney. The bowel should be closed in layers, although this is not necessary if the opening is so small that it cannot be identified.

## REFERENCES


1. Ellik, M. and Getz, J.: Nephrocolonic fistula: A dual case study. J. Urol. 70:364 (September) 1953.
2. Abeshouse, B. S., Robbins, M. A., Gann, M. and Salik, J. O.: Intestinovesical fistulas; report of seven cases and review of the literature. J.A.M.A. 164:251 (May 18) 1957.
3. Bors, E. and Kudish, H. G.: Intestinovesical fistula: Report of six cases. J. Urol. 72:365 (September) 1954.
4. Goodwin, W. E., Winter, C. C. and Turner, R. D.: Replacement of the ureter by small intestine: Clinical application and results of the "ileal ureter." J. Urol. 81:406, 1959.
5. Burkholder, T.: Personal communication.
6. Nourse, M. H.: Personal communication.
7. Goodwin, W. E., Turner, R. D. and Winter, C. C.: Rectourinary fistula: Principles of management and a technic of surgical closure. J. Urol. 80:246, 1958.
8. Collins, C. G. and Jones, F. B.: Preoperative cortisone for vaginal fistulas. Obst. & Gynec. 9:533 (May) 1957.

# Implications of Maximal Bacterial Resistance to Antibiotics

HARRY SENECA* AND O. K. TROC†

*Columbia University College of Physicians and Surgeons, New York*

*Widespread use of antibiotics is accelerating the production of antibiotic-resistant bacteria.*

*Resistance is primarily a genetic phenomenon, but environment is also important.*

*Certain pathogenic bacteria have the genetic potential of mutation and may be troublesome to future generations of mankind.*

*Studies on antibiotic-resistant bacteria indicate maximal limits of tolerance of commonly used antibiotics and of serial viability of bacterial cultures in relation to antibiotics.*

NATURALLY occurring populations of bacteria are never homogenous, but consist of many different and distinguishable types of cells, even when such cultures consist of only one strain or are descendants of one single cell.[1] The mechanism of this change is thought to be the gene mutation inherent in the bacteria.[2] Mutation rates are a function of generation time and population size. The generation time of bacteria is short compared with that of higher plants and animals. Populations of bacteria usually contain millions or billions of individuals. The total rate of gene mutation among pathogenic bacteria is high. Each gene is said to mutate to a different stable form at a constant rate averaging one per million cells in each generation. The number of genes in all organisms is probably between 1000 and 10,000. Therefore, a colony of one million cells, whose generation time is 24 hours, could give rise to several thousand different mutants daily, of which a few could be resistant to chemotherapy.[3]

*Assistant Professor, Department of Urology; †Technician, Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital, New York, New York.

The in vitro implications of variation in bacterial species have been rather thoroughly explored from both the genetic and the biochemical viewpoints. Some of our most useful industrial processes depend on selective utilization of bacterial variations. The successive increase of bacterial invasiveness in human infections has not been extensively studied; yet, it is vital to therapeutic problems created by drug-resistant bacteria. Attempts to correlate bacterial resistance to antibiotics with invasive-

ness have not been directly made with pure species. However, general patterns do emerge from previous studies of bacteria in experimental infections such as peritonitis or genitourinary infections.

The fortuitous inability of the gonococci to escape from control by penicillin, at the same time that they are resistant to the sulfonamides, took place within a few months after general introduction of the sulfonamides had contributed largely to the drop in this type of infectious disease. The implications of variations in invasive infectiousness due to drug therapy or to variations in the host have been extensively studied in acid-fast bacteria, but have not, as far as is known, been applied to pathogenic organisms in the genitourinary tract. If invasive infectiousness is influenced by variations in the host, then, to some extent, the host by his natural resistance may act as a drug might in screening out and destroying those organisms sensitive to the host's natural positive resistance. The increased virulence resulting from animal passage may, in some subtle way, reflect the selection of those mutants most likely to destroy the host. This in a way is a self-limiting process, whereas resistance to drug therapy may not be. Obviously, if the host's resistance becomes too high, no infection occurs, and bacterial multiplication decreases. If the host's resistance is too low, the organisms are cut off in their homeland. More subtle changes in bacteria, such as the spontaneous changes in severity of scarlet fever, may be reflections of this sort of oscillating solution to two variables simultaneously, one variable being the bacterial species's rate of mutation, the second being the availability of a susceptible pool of host. It has been shown that some drugs are able to increase mutation rates, and in some instances the mutations give rise to more resistant species. As far as is known, the converse situation—that there might be materials in nonmutating species that would serve as inhibitors to mutations in other species—has not been explored. It has been pointed out that, if this latter type of host-induced mutation takes place, antimutagenic substances may well be of considerable value in decreasing bacterial invasiveness. The theoretical relationship of in vitro and in vivo susceptibility or resistance to drugs, or both, is discussed in the appendix to this paper.

Although drugs do not originate bacterial resistance to antibiotics or other agents, they may act as selective "filters," which eliminate or destroy the sensitive cells and leave the resistant cells to multiply freely. Thus, the chemotherapeutic agents act as do any other selective forces in the environment. The antibiotic era has seen a widespread emergence of resistant organisms and bacteria. The continued use of antibiotics will aggravate this serious situation, unless members of the medical profession adopt rational measures to combat or control bacterial resistance.

Clinically speaking, there are two types of resistance to antibiotics. One type is characterized by the evolution of resistance in a patient during the course of treatment. In these cases, the antibiotic therapy initially controls the pathogenic bacteria, but becomes ineffective as the patient relapses into an antibiotic-resistant infection. This type of resistance results from the development of new mutations resistant to the antibiotic within the population of pathogenic bacteria harbored by the patient. Endocarditis caused by alpha *Streptococcus* is an example of this type of mutation. The second type of resistance develops more slowly, involves larger populations of pathogenic or potentially pathogenic bacteria, and is not restricted to a single patient. It is characterized by a gradual increase, over a period of years, in resistant strains in a given hospital or clinic and is associated with the widespread use of antibiotics. This type is the result of the gradual accumulation of mutants which are maintained in the reservoir of bacteria about a hospital. When the use of antibiotics is carefully restricted, the number of resistant strains may gradually decrease.

These two types of bacterial resistance or mutation may be distinguished genetically. The rapid type is usually the result of a single mutation, while the slow type is the result of multiple progressive mutations. Although this is rather difficult to demonstrate clinically, in the laboratory resistance develops slowly in

"stepwise" increments, while rapid resistance develops in one abrupt transformation.[4,5]

During the course of antibiotic therapy, the potent antibiotics may eliminate or kill the bacterial flora of the intestinal and upper respiratory tracts and the vagina. *Candida albicans*, a natural inhabitant, is resistant to antibiotics and grows unopposed. It may give rise to candidiasis or moniliasis of the colon, rectum, mouth, respiratory tract, vagina, skin or mucous membranes. Although in most cases discontinuing antibiotic therapy gives relief to the patient, in rare cases systemic or generalized candidiasis may be a serious or even fatal complication.[6-9] Nystatin is recommended for treating local candidiasis. Amphotericin B has recently been reported to be effective in experimental generalized candidiasis in mice.[10] Infection with antibiotic-resistant micrococci, resulting in micrococcal enterocolitis, has become so important in recent years that the *Journal of the American Medical Association* dealt with it editorially in 1954[11] and 1955.[12] Infection with *Proteus vulgaris (Bacillus proteus)* and *Pseudomonas aeruginosa* during the course of antibiotic therapy was first reported in 1952.[13]

The present studies were carried on to determine the maximal limit of tolerance or resistance of *Micrococcus pyogenes aureus* to penicillin; of *P. vulgaris, Ps. aeruginosa, Aerobacter aerogenes* and *Escherichia coli* to tetracycline; of *Str. pyogenes* to penicillin, and of *Str. faecalis* to penicillin as well as to tetracycline.

### *Material and Methods*

*Source of cultures*—Antibiotic-resistant strains of *M. pyogenes aureus, Ps. aeruginosa* and *P. vulgaris* were obtained from various medical centers in the United States. Strains of *A. aerogenes, Esch. coli, Str. pyogenes* and *Str. faecalis* were obtained from patients at the Columbia-Presbyterian Medical Center in New York.

*Induction of resistance*—Brain-heart infusion broth was used routinely in these experiments. In the case of *Str. pyogenes,* human serum or plasma was added to the broth. The minimal inhibitory concentration (MIC) in units or gamma per milliliter of the antibiotic for each culture was first determined by the tube dilution method. A subinhibitory concentration of the antibiotic was added to 5 ml. of broth, and 0.1 ml. of bacterial culture was inoculated. The tubes were incubated for a period of 7 to 10 days. Subcultures were either serially made using the same concentration of the antibiotic, or the concentration of the antibiotic was increased gradually, depending on the growth. Where the growth was inhibited in a given concentration of the antibiotic, the concentration was reduced. Previous generations or earlier cultures were never discarded, because viable bacteria were constantly available for future experimentation. Subcultures were made every 7 to 10 days. Since no specific rules could be followed, the concentration of the antibiotic was determined by trial and error. The experiments lasted two to three years, and there were two end points: (1) the maximal limit of tolerance of the antibiotic and (2) the maximal limit of serial viability of the culture in relation to the antibiotic. We have reached the end points in our studies on *M. pyogenes aureus, P. vulgaris, Ps. aeruginosa, Esch. coli* and *Str. pyogenes.* Studies are still in progress on *A. aerogenes* and *Str. faecalis.*

*Cross resistance of superresistant experimental strains to other antibiotics*—The drugs used in these studies included penicillin, tetracycline, oxytetracycline, chloramphenicol, streptomycin, novobiocin, erythromycin, polymyxin B sulfate, bacitracin, neomycin, carbomycin, sulfadiazine and FURADANTIN®. The minimal inhibitory concentration of these drugs was determined for the original stock strains and for the experimental super penicillin-resistant strains of *M. pyogenes aureus* and the super tetracycline-resistant strains of *P. vulgaris* and *Ps. aeruginosa.*

### *Results*

*M. pyogenes aureus*—Of the numerous strains studied, seven could be serially cultured in 50,000 units per milliliter of penicillin and six in 20,000 units per milliliter. In other words, *Micrococcus* could be maintained viable serially in a maximum of 50,000 units

per milliliter of penicillin. Most strains perished in 500 to 1000 units per milliliter. Although a few strains survived for a brief period in 75,000 units per milliliter penicillin, in this concentration they were not viable on serial passage. The seven strains which became resistant to 50,000 units per milliliter of penicillin were studied to determine their cross resistance to other antibiotics and antibacterials. There was some increase, up to sixteenfold, in their cross resistance to streptomycin, penicillin-streptomycin, tetracycline, oxytetracycline, chloramphenicol, polymyxin B sulfate, erythromycin and carbomycin. No significant change or increased resistance was manifested to neomycin, bacitracin, novobiocin, Furadantin and sulfadiazine.[14]

*P. vulgaris and Ps. aeruginosa*—Thirty strains of *P. vulgaris* were tested against tetracycline. Eight strains (48, 189, 233, 271, 1617, 1905, 32500 and M) could be maintained viable in 3000 μg. per milliliter of tetracycline, and a few strains survived temporarily in 8000 μg. per milliliter.

Five strains of *Ps. aeruginosa* (2, 315, 324, 1621 and 2868) could be maintained viable serially in 3000 μg. per milliliter of tetracycline, and a few strains survived temporarily in 8000 μg. per milliliter.

Studies on the cross resistance to other antibiotics and antibacterials of the tetracycline-resistant strains of *P. vulgaris* and *Ps. aeruginosa* did not reveal any trends or changes of resistance.

*A. aerogenes and Esch. coli*—Studies on 10 strains of *A. aerogenes* (193, 209, 222, 223, 226, 240, 243, 247, 249 and 319) are not yet concluded. However, so far these strains have been viable in 950 μg. per milliliter of tetracycline, and the titer is still increasing. Eight strains of *Esch. coli* (21, 237, 239, 244, 264, 279, Julian and Maddi) survived serially in 50 to 100 μg. per milliliter of tetracycline. Although a few reached a titer of 250 μg. per milliliter of tetracycline, all perished above this concentration.

*Str. pyogenes and Str. faecalis*—*Str. pyogenes* could not tolerate increasing concentrations of penicillin or tetracycline and perished in concentrations of less than 25 units or gamma per milliliter of the antibiotics. *Str. faecalis* was somewhat more tolerant and survived temporarily in a concentration of 80 units of penicillin or 80 μg. tetracycline.

### *Discussion*

If the present trend in the evolution of bacterial mutation continues as a result of the promiscuous use of antibiotics, it is apparent that man is accelerating the rate of production of antibiotic-resistant strains of bacteria. Resistance is primarily a genetic phenomenon, but environment plays an important role as well. It is obvious from these findings that not all bacteria have the genetic tendency to mutate. For example, *Esch. coli*, *Str. pyogenes* and *Str. faecalis* do not mutate. Probably these organisms will not be sources of trouble to future generations of physicians. On the other hand, *M. pyogenes aureus*, *P. vulgaris*, *Ps. aeruginosa* and *A. aerogenes* have the genetic potential of mutation and, therefore, may cause much trouble to future generations of mankind. It is suggested that the mutational tendencies of all pathogenic and potentially pathogenic bacteria be determined so that we may be able to predict the future events in the host-parasite relationship.

### *Summary*

1. *M. pyogenes aureus* is serially viable in a concentration of 50,000 units per milliliter of penicillin, but it can survive temporarily in 75,000 units per milliliter.

2. *P. vulgaris* and *Ps. aeruginosa* can survive serially in a concentration of 3000 μg. per milliliter of tetracycline, but they survive temporarily in 8000 μg. per milliliter.

3. *A. aerogenes* is able to survive serially in a concentration of 950 μg. per milliliter of tetracycline.

4. *Esch. coli* survives in a concentration of 50 to 100 μg. per milliliter of tetracycline, but the maximal limit of tolerance is 250 μg. per milliliter.

5. *Str. faecalis* can survive in a maximal concentration of 80 units per milliliter of penicillin or 80 μg. per milliliter of tetracycline, and *Str. pyogenes* survives in 25 units or μg. per milliliter.

6. Penicillin-resistant strains of *M. pyogenes aureus* show increased cross resistance to other antibiotics, but not to neomycin, bacitracin, novobiocin and other antibacterials. Tetracycline-resistant strains of *P. vulgaris* and *Ps. aeruginosa* manifest increased resistance to other antibiotics or antibacterials. The factors which determine these points of resistance to drugs deserve further study.

7. A pseudoalgebraic development of the types of study is likely to be most fruitful in clinical attack on future resistant strains.

## APPENDIX

Let us establish a relation of in vitro to in vivo effects:

If

S = drug susceptibility in vivo
S′ = drug susceptibility in vitro
V = virulence of organism at standard inoculum in standard location in standard host

Then

1. $S = KS'/V$, where K will be the same for standard inoculum organism, host and location.

Let us analyze V further:

Let

m = mutation rate
$\gamma$ = per cent total population of inoculum actively invasive
p = rate of production of active exogenous product promoting invasion or resisting destruction due to natural resistance
i = degree or lack of contact with this host or this drug of this organism
d = degree of reactive response occasioned by this organism in this host antagonistic to the organism

Then

2. $V = \frac{\gamma pm}{id}$ and as $S = \frac{KS'}{V} = \frac{KS'id}{\gamma pm}$

Now S′ may be similarly analyzed:

Let

r = rate of multiplication
m = mutation rate
a = fraction of metabolic requirement which is entirely drug-susceptible

Then

3. $S = \frac{r}{ma}$

Putting (2) and (3) into (1) we get

$$S = KS' = K\frac{\frac{r}{ma}}{\frac{pm}{id}}$$

$$= K\frac{rid}{m^2ap}$$

Now let us presume rate of mutant production is a fraction $\beta$ of total growth rate.

Then

$m = r\beta$ and

$$S = K\frac{id}{\beta a^2 \gamma p}$$

Now $\gamma$, the per cent actively invasive, is also a function of the growth rate, as the per cent of active invaders in a rapidly increasing population will increase with the rate of increase, so that:

$\gamma = fr$ where f is a constant fraction of the new organisms

Then

$$S \text{ becomes } K\frac{id}{\beta^2 ra^2 fp} K'\frac{id}{\beta^2 ra^2 p} \text{ of } \frac{K}{f} = K'$$

Similarly, we may presume that p, the rate of production of exo-enzyme or capsular substance, is related to the degree of local reaction of the host and to the growth rate in some such fraction as $d = kpr$.

Then

$$S \text{ becomes } K''\frac{i}{\beta^2 ra} \text{ of } K'/kpr$$

In turn, a, the fraction of metabolic requirement drug-insusceptible, will be a constant, which will regulate r in a given strain in a given environment as it limits the rate of uptake and synthesis of the organism.

Let

$K''/a = K'''$

Then

$$S = K'''\frac{i}{\beta^2}$$


## ACKNOWLEDGMENT

Thanks are due to Dr. Hans H. Zinsser for the following discussion of the material in the appendix.


### *Comment by Dr. Zinsser*

The dominant facts in vivo are i and even more so $\beta$. It can be seen that an organism's susceptibility to antibiotic attack in vivo varies directly as its lack of exposure to the environment and inversely as the square of its mutation rate.

The form of dependence on other variables can be rendered considerably more sophisticated, but it is unlikely that other emphasis is significant.

If the results of this development are to be trusted, investigative focus should be directed at inhibition of mutation by whatever agents suggest themselves.

This suggests, further, that prophylactic chemotherapy may be justified, because it will attack the organism when the latter's susceptibility is greatest and before hostile conditions

have influenced it. The results of the study give some basis for avoiding radiation in infection and suggest that, in the face of antibiotics, the growth rate itself may not be entirely a dominant factor in clinical infection.

## REFERENCES


1. Beadle, G. W.: Biochemical genetics. Chem. Rev. 37:15, 1945.
2. Tatum, E. L.: Induced biochemical mutations in bacteria. Cold Spr. Harb. Symp. Quant. Biol. 11:278, 1946.
3. Muller, H. J.: The gene. Proc. Roy. Soc. London s.B 134:1, 1947.
4. Bryson, V. and Demerec, M.: Patterns of resistance to antimicrobial agents. Ann. New York Acad. Sc. 53:283, 1950.
5. Cavalli, L. L. and Maccacaro, G. A.: Chloromycetin resistance in *E. coli*, a case of quantitative inheritance in bacteria. Nature, London 166:991, 1950.
6. Woods, J. W., Manning, I. H., Jr. and Patterson, C. N.: Monilial infections complicating therapeutic uses of antibiotics. J.A.M.A. 145:207, 1951.
7. Moore, M.: In vitro and in vivo effect of Aureomycin on *Candida albicans*. J. Lab. & Clin. Med. 37:307, 1951.
8. Paine, T. F., Jr.: In vitro experiments with *Monilia* and *Escherichia coli* to explain moniliasis in patients receiving antibiotics. Antibiotics & Chemother. 2:653, 1952.
9. Kligman, A. M.: Are fungus infections increasing as a result of antibiotic therapy? J.A.M.A. 149:979, 1952.
10. Sternberg, T. H., Wright, E. T. and Oura, M.: A new antifungal antibiotic, Amphotericin B. Antibiotics Annual 1955-1956. New York, Medical Encyclopedia, Inc., 1956, p. 566.
11. Editorial: Antibiotic-resistant micrococci (staphylococci). J.A.M.A. 156:608, 1954.
12. Finland, M.: Antibiotic-resistant micrococci infections (Editorial). J.A.M.A. 158:188, 1955.
13. Yow, E. M.: Development of *Proteus* and *Pseudomonas* infections during antibiotic therapy. J.A.M.A. 149:1184, 1952.
14. Seneca, H., Lattimer, J. K. and Troc, O. K.: Some implications of increasing antibiotic resistance of *Micrococcus pyogenes aureus*. A.M.A. Arch. Path. 64:481, 1957.


# MEETINGS *and Postgraduate Courses*

New England Postgraduate Assembly, Boston: Seventeenth annual assembly, November 3-5, at the Statler Hilton. For further information, write to: Dr. Joseph R. Frothingham, Chairman, New England Postgraduate Assembly, 22 Fenway, Boston 15.

New York University-Bellevue Medical Center Post-Graduate Medical School, New York: Postgraduate review courses 1959-60:

Surgery of the biliary tract and pancreas, November 2-6
Surgery of the colon and rectum, November 9-13
Surgery of the head and neck, including the thyroid, November 16-20
Abdominal surgical diseases in children, November 23-25

Courses in arthritis and related disorders for the general physician, November 9-13 and May 16-20, and for the experienced clinician and research worker, March 14-18. For further information, write to: Office of the Associate Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16.

Second International Meeting of Forensic Pathology, New York: To be held September 18-21, 1960. Meeting will include dedication of the new building for the Office of the Chief Medical Examiner, City of New York. For further information, write to: Dr. Milton Helpern, 55 East End Avenue, New York 28; Dr. Charles Larsen, Tacoma General Hospital, Tacoma 5; or Dr. Francis E. Camps, 37 Welbeck Street, London W.1, England.

University of Kansas School of Medicine, Kansas City: Postgraduate courses for 1959-1960:

Fractures, November 23-24
Glaucoma, December 11-12
The heart: Rheumatic and congenital heart disease, January 18-21
Radiology and radioactive isotopes, February 8-10
The ophthalmoscope: Its use in medicine, February 11
Hematology, February 22-26
Pediatrics, March 7-9
Medical-surgical subspecialties symposia:
  Pulmonary disease, March 21
  Gastroenterology, March 22
  Psychiatry, March 23
  Neurology and neurosurgery, March 24
  Endocrinology and metabolism, March 25
Ophthalmology, April 4-6
Otolaryngology, April 6-8
Anesthesiology, April 11-13
Respiratory physiology in childhood, April 21-22
Surgery, May 23-26

For further information, write to: William D. Nelligan, Executive Director, Department of Postgraduate Medicine, University of Kansas Medical Center, Kansas City.

# Special Considerations Regarding Fractures in Children

CHARLES H. HERNDON*

*Western Reserve University School of Medicine, Cleveland*

*Many fractures of actively growing bone heal fairly well even with indifferent treatment, but others may terminate disastrously unless expertly handled.*

*The general practitioner should know well the principles and methods of treatment of those fractures he will deal with most commonly, recognize the limitations of his technical capabilities, and refer to the nearest fracture center the more complicated fractures. Referral is more often indicated because of possible complications than because of the difficulties of initial definitive treatment.*

THREE of the factors of primary importance in dealing with fractures in the younger age group are (1) the difference in physiologic response to trauma of active, growing bone compared with mature, relatively static bone, (2) the effect of trauma on epiphysial growth, and (3) the relative degree of scarring and contracture of joint capsule and muscles following trauma in a child compared with that in an adult.

CHARLES H. HERNDON

### *Physiologic Response to Trauma*

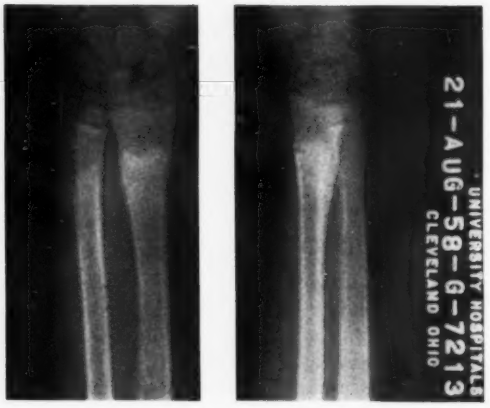
Osteogenesis and osteoclasia are more active in growing bone than in adult bone, which is relatively static and demonstrates only slow resorption and regeneration of osteogenic tissue. This is particularly true in the metaphysis but is also true in the compacta of the shaft. The response to fracture or trauma is therefore more rapid in growing bone with more active callus formation. Apparently more osteogenic cells are immediately available to produce osteoid tissue without the necessity of metaplasia. This difference in the physiologic response of growing bone to trauma has the following important implications in regard to fracture healing.

*1. More rapid healing*—A fracture in a

*Associate Professor of Orthopedic Surgery, Western Reserve University School of Medicine, Cleveland, Ohio.

Presented before the forty-third annual Assembly of the Interstate Postgraduate Medical Association at Cleveland.

FIGURE 1. Patient A. W., age nine years. Fracture of both bones of the forearm caused by a fall on the outstretched hand, June 13, 1958. Fracture was reduced by closed manipulation and immobilized in a circular plaster cast from above the elbow to the distal palmar crease. Note the rapidity of healing and the firm bony union with excellent remodeling within a period of nine weeks.




child not only heals much more rapidly than a similar fracture in an adult, but there is also little likelihood of nonunion. Figure 1 demonstrates the rapidity of bone healing in a child, nine years of age, who fractured both bones of the forearm on June 13, 1958. The fracture was reduced by closed manipulation and the forearm was immobilized in a circular plaster cast from above the elbow to the distal palmar crease. Firm bony union with excellent remodeling occurred within nine weeks. A similar fracture in an adult undoubtedly would require a longer time to heal.

*2. More complete remodeling*—In addition to more rapid healing, one may anticipate more active remodeling of growing bone than of adult bone. In certain instances, therefore, more angular deformity may be accepted with the expectation that the deformity will disappear with further growth. Figure 2 demonstrates x-rays of the right wrist of a four year old girl who fractured the distal radial metaphysis on September 11, 1957. The fracture was not completely reduced and further angulation occurred during the course of plaster immobilization. By March 1958, however, after approximately six months, the deformity was almost completely corrected by remodeling in the metaphysial area.

The greatest degree of spontaneous correction of angular deformity occurs when the fracture is in the plane of motion of a neighboring hinge joint. Angulation in other directions may persist and should never be accepted in the treatment of fractures. Rotational deformities are almost invariably permanent and should never be accepted. It may also be stated that the younger the child and the nearer the fracture to the end of the bone, the more angulation one may accept. The older the child and the nearer the fracture to the middle of the bone, the more accurate the reduction must be (figure 3). There are, according to Blount,[1] three variables to keep in mind: the age of the child, the distance of the fracture from the end of the bone, and the amount of angulation.

*3. Effect on linear growth*—Although the mechanism is not clear, it is an established fact that a fracture through the shaft of a long bone tends to stimulate linear growth of the injured bone. This is particularly true if the fracture is through the metaphysial area. This overgrowth is similar to the growth stimulation observed when osteomyelitis affects the metaphysial area of a growing bone. It is well to keep this fact in mind and often accept a bayonet-type apposition in the reduction of

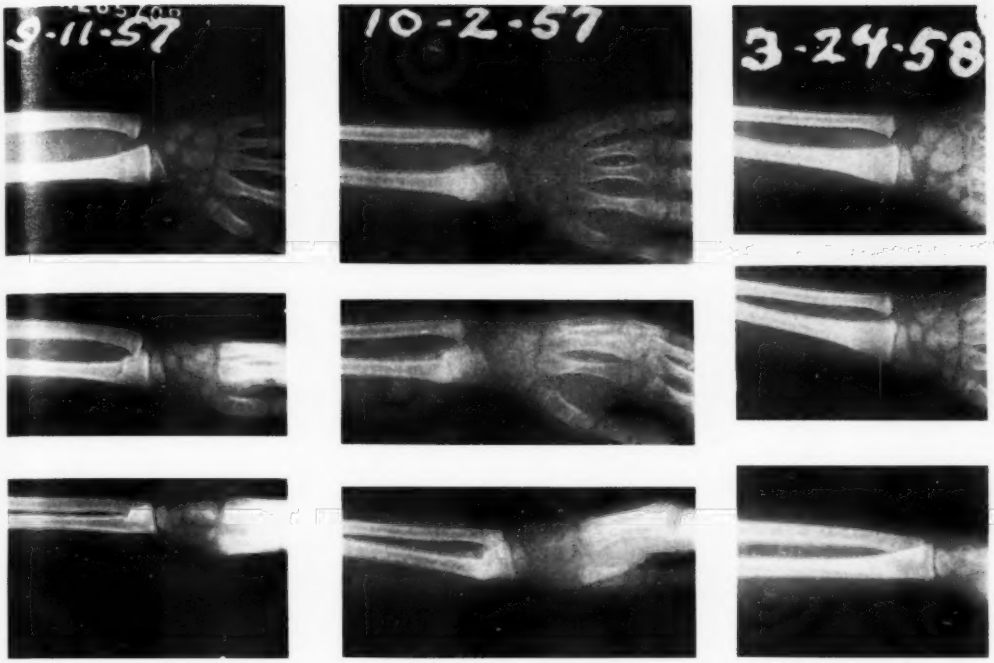



FIGURE 2. Patient L. S., age four years. Fracture of distal radial metaphysis caused by fall on the outstretched hand, September 11, 1957. Fracture was inadequately reduced and further angulation occurred while it was in a plaster cast, but note the excellent remodeling and spontaneous correction of the deformity by March 24, 1958, a period of approximately six months.

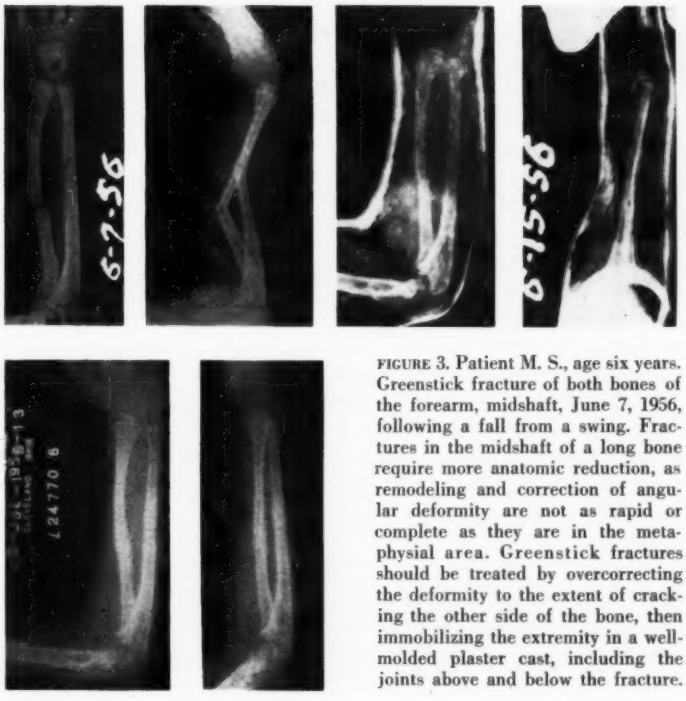



FIGURE 3. Patient M. S., age six years. Greenstick fracture of both bones of the forearm, midshaft, June 7, 1956, following a fall from a swing. Fractures in the midshaft of a long bone require more anatomic reduction, as remodeling and correction of angular deformity are not as rapid or complete as they are in the metaphysial area. Greenstick fractures should be treated by overcorrecting the deformity to the extent of cracking the other side of the bone, then immobilizing the extremity in a well-molded plaster cast, including the joints above and below the fracture.

FIGURE 4. Patient R. C., age 11 years. Fracture of the midshaft of the femur, November 16, 1953. Fracture was treated by means of balanced suspension traction until union was moderately advanced, and then plaster spica immobilization was employed until consolidation was complete. Bayonet apposition was accepted. The fracture stimulated linear growth so that although slight overriding was present, leg lengths are now equal and function has returned to normal.

a fracture of the shaft of a long bone. This often is not only acceptable but at times even desirable up to 10 years of age in girls and 12 years of age in boys. The amount of growth stimulation is proportional to the initial displacement and the amount of callus. It has been observed that if one remanipulates a fracture after callus is forming, more exuberant callus formation may follow and almost inevitably a concomitant stimulation to excessive growth.

Figure 4 demonstrates x-rays of the femur of an 11 year old boy who fractured the midshaft on November 16, 1953. The fracture was treated by means of balance suspension traction until union was moderately advanced, and then the extremity was immobilized in plaster until consolidation was complete. Note that bayonet apposition was accepted with slight overriding. One year after the fracture, the length of the legs was equal and the function was normal.

Trauma to bone of any type may stimulate linear growth. Accordingly, operative intervention in the treatment of the shaft of a long bone may further stimulate linear overgrowth. An example is given in figure 5, showing fractures of the midshaft of the femur and of the proximal end of the tibia in an eight year old boy who was struck by an automobile. The surgeon thought the tibial fracture could not be controlled unless the femur was stabilized. Therefore, the fracture of the femur was reduced and a Rush nail inserted. Both fractures healed promptly, but the extremity is now ¾ in. longer than the opposite leg due to overgrowth stimulated by the fracture in the metaphysis of the tibia as well as the fracture of the midshaft of the femur with superimposed operative trauma.

Figure 6 represents a situation which actually is more acceptable. An eight year old boy fractured the shaft of the femur on August 9, 1957. Hospitalization and treatment by means of balanced suspension traction were refused, and the extremity was immobilized in a plaster spica. Overriding and angulation occurred at the fracture site, but consolidation and reorganization were excellent. The boy's legs are equal in length and he has entirely normal function.

The fact that an operative approach on growing bone will stimulate linear growth is reason enough to contraindicate open reduc-

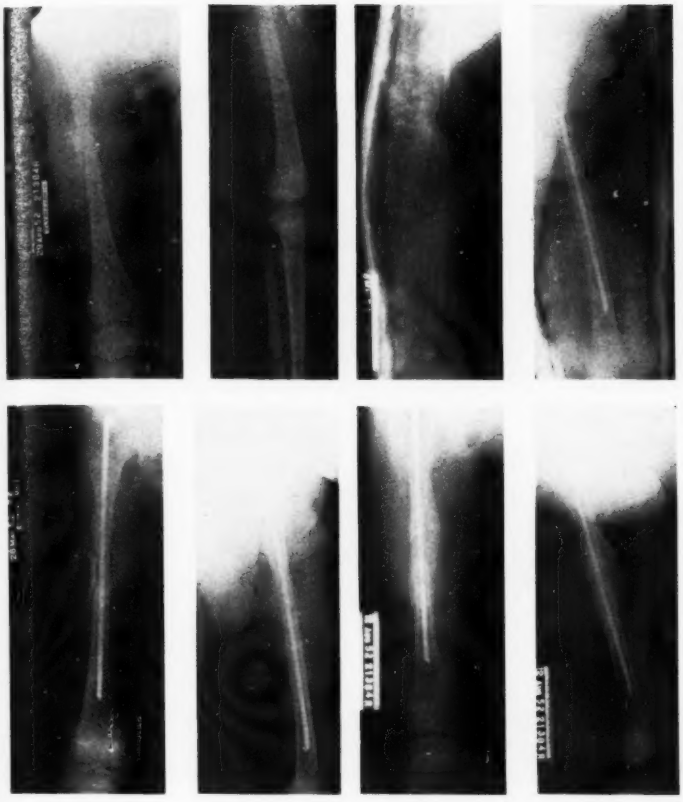


FIGURE 5. Patient R. J., age eight years. Transverse fracture through the midshaft of the femur and a comminuted fracture through the proximal tibial metaphysis, March 1952. Patient was struck by an automobile. The surgeon elected to treat the fractured femur by intramedullary nail fixation and the fractured tibia by plaster cast immobilization. Anatomic alignment was achieved and the fractures healed satisfactorily, but there was a residual overgrowth of the extremity of ¾ in. due to stimulation of linear growth by the fractures and operative trauma.

FIGURE 6. Patient R. B., age eight years. Transverse fracture through the shaft of the femur, August 9, 1957. Hospitalization and balanced suspension traction were refused, and the patient was treated by plaster spica immobilization. Moderate angulation and overriding of the fragments in plaster resulted, but note the reorganization and excellent consolidation at the fracture site within a nine month period. This boy's legs are now equal in length and he has normal function, the equalization of leg length being caused by the stimulation of linear growth by the fracture.

FIGURE 7. Three types of epiphysial injury: a single epiphysial separation without metaphysial fracture; an epiphysial separation with a fracture including a triangular fragment of metaphysis; a comminuted fracture extending through the central portion of the epiphysis up into the metaphysis.

tion of fractures in children except in the most unusual circumstances. There are other even more important objections, however. Open reduction of a fracture in a child is almost always totally unnecessary. These fractures will heal and will heal rapidly. Open reduction creates the possibility of infection. It necessitates needless stripping of the periosteum at the fracture site, thereby reducing the vascular supply of the bone ends and leading to the possibility of delayed union or nonunion. The only fractures in children that demonstrate difficulty in healing are those in which ill-advised open reductions have been done or those in which infection has developed either from compound wounds or after open reductions.

### *Effect of Trauma on Epiphysial Growth*

There are three possible types of damage to the growth line (figure 7). One is caused by straight compressive force through the epiphysis, producing linear fractures that extend through the epiphysis, the epiphysial line, and the metaphysis. The epiphysial plate itself is almost invariably damaged, and growth disturbances following this type of injury are common. A second type of injury is charac-

FIGURE 8. Patient L. W., age 13 years. Epiphysial fracture of the distal end of the radius, May 7, 1958. Note the small triangular fragment of the metaphysis that was displaced with the distal epiphysis. Although anatomic reduction was not achieved, complete remodeling and normal-appearing epiphysial line were present five months later.

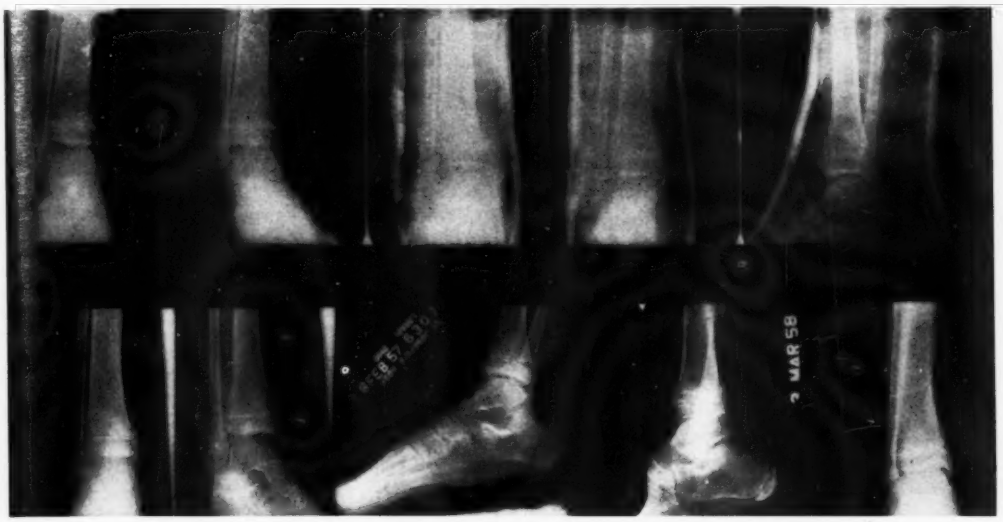


FIGURE 9. Fracture of medial malleolus extending into the distal tibial epiphysial plate, January 14, 1957. Note that although anatomic reduction was achieved there is evidence of asymmetric closure of the distal tibial epiphysis on the medial side as early as March 1957, two or three months following injury. By November 1957, definite asymmetric closure is apparent with the development of ankle varus of such an extent that osteotomy of the tibia to correct the deformity was indicated.

terized by a separation of the epiphysial plate with a small fragment of the metaphysis fracturing and being displaced with the epiphysis. In this type of epiphysial separation the epiphysial plate invariably remains attached to the epiphysis rather than the metaphysis. Therefore, if accurate reduction is achieved with gentleness, there is a strong probability that growth will be normal. The third type of injury is characterized by a simple epiphysial separation without demonstrable fracture in the metaphysis or epiphysis. Again the epiphysial plate remains attached to the epiphysis and is displaced with it. If reduction is achieved with gentleness, there may be no disturbance of growth. It is apparent that the more traumatic the reduction, the more likely it is that growth disturbances will result. Open reduction in these situations is contraindicated. One would accept a moderate amount of displacement rather than carry out repeated forcible manipulations or open reduction. Reduction should be achieved by traction and gentle manipulation, attempting to prevent grinding the epiphysial plate against the metaphysis during the maneuver.

Figure 8 shows x-rays of a 13 year old girl with a separation of the distal radial epiphysis associated with a small triangular fracture of the metaphysis, this fragment being displaced with the distal radial epiphysis. Reduction was carried out by traction and gentle manipulation. Perfect anatomic reduction was not achieved, but rather than subject the patient to repeated manipulations the deformity was accepted. Within five months, complete reorganization and remodeling occurred, and comparative x-rays of the right and left wrists demonstrate complete restoration of anatomy.

Figure 9 is an example of a more serious type of epiphysial injury, caused by compressive forces that extend up through the epiphysial plate. The child fell from a height and landed on his foot, which then rocked into inversion, causing a fracture which extended up through the medial malleolus, the epiphysis, and the epiphysial plate. The surgeon was able to achieve almost an anatomic reduction, but in spite of this there was asymmetric closure of the medial aspect of the distal tibial epiphysis resulting in marked ankle varus which required a corrective osteotomy.

### *Effect of Scarring on the Capsule and Muscles*

The third important factor in treating fractures in children is the effect of scarring on the capsule and muscles. The older the patient, the more difficult it is to regain joint motion following immobilization. A child's joint may be immobilized for several months and normal motion may be expected within a very short time after immobilization is discontinued, whereas in an adult stiffness and pain might be serious problems. Even though a fracture may be fairly near the joint, immobilization in a child is not of serious significance. Of course, if the fracture actually extends into the joint, mobilization will be more difficult, but even in this situation motion is regained much more readily than in an adult. We are therefore permitted to and should immobilize an extremity more completely in a child than we dare to in an adult. A child is much more active and usually less reliable; therefore a more complete fixation is indicated. It is important always to immobilize a joint on each side of the fracture. One does not hesitate even to immobilize the metacarpophalangeal joints to secure complete fixation at the wrist joint. It is also important to maintain the immobilization until union is completely mature and until unrestricted activity at play may be permitted without fear of refracture. There is no urgency about removing fixation in a child, as joint function returns quickly, but because of the rigors of normal play activity it is important that the fracture be solidly united before immobilization is discontinued. In this regard it should be emphasized that unrestricted play activity is the best form of physical therapy, and the best physical therapist is a companion of the playfield. Once the cast is removed, heat and massage are practically never indicated, and formal physical therapy in most instances not only is unnecessary but might well be harmful in restoration of joint motion. Stretching is contraindicated in attempting to regain joint motion following any fracture in a child.

FIGURE 10. Patient A. B., age three years. Compression fracture through the distal end of the tibia including the epiphysis and epiphysial line, January 3, 1958. Healing was prompt and complete. Comparative x-rays made October 30, nine months later, show no change in growth manifestations.

FIGURE 11. Patient E. P., age nine years. Comminuted fracture through the central portion of the distal end of the right femur occurred at the age of seven years. Healing occurred with the fragments in good alignment, but premature closure of the epiphysis resulted, with development of marked discrepancy in leg length as indicated in the anteroposterior x-ray of both knees.

### *Conclusion*

The fact that many fractures of actively growing bone heal fairly well even with indifferent treatment might lead the unwary to neglect the fact that other fractures may terminate disastrously unless expertly handled. Which fractures, then, should a general practitioner accept for treatment? My answer would be that the general practitioner who accepts fractures for treatment should not only know well the principles and methods of treatment of those fractures with which he will have to deal most commonly and recognize the limitations of his technical capabilities, but also recognize the more complicated fractures at once and, after first-aid treatment, send them without delay and without a preliminary period of improper or ineffective treatment to the nearest fracture center where special training, experience and technical skill are readily available.

The criticism which the general practitioner incurs with respect to fracture treatment is due to ineffective attempts to treat cases beyond his capabilities. The argument of necessity rarely applies now, as it has become well established that a patient, even though seriously injured, may be transported long distances to a fracture center without deleterious effect provided the fracture is properly splinted and adequate treatment for shock is given prior to transportation. There is scarcely any location in the United States today that is not within a few hours' distance of a well-equipped fracture service. The physician must consider both the early and the late complications of the fractures as well as the technical difficulties involved in the immediate definitive treatment in determining whether or not he should accept the patient for treatment. Referral is more commonly indicated because of the possible complications than because of the difficulties of the initial definitive treatment. Fractures in children carry all the potential complications of fractures in adults, and in addition there is the potential difficulty of growth disturbances.

REFERENCES


1. Blount, W. P.: Fractures in Children. Baltimore, The Williams & Wilkins Company, 1955.
2. Herndon, C. H.: Fractures and dislocations. In Cecil, R. L. and Conn, E. F. (ed.): The Specialties in General Practice. Ed. 2. Philadelphia, W. B. Saunders Company, 1957.



1959

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Nov. 2-5 Palmer House Chicago, Illinois

New Concepts in the Treatment of Diabetes

The availability of an ever-increasing number of oral hypoglycemic agents has led to a broader and more effective means of controlling diabetes mellitus. A comparison of the modes of action, pharmacology, relative effectiveness, and toxicity of tolbutamide, chlorpropamide, metahexamide and phenformin will be presented in the light of experiences obtained in treating more than 400 patients.

GEORGE J. HAMWI, M.D.

Professor of Medicine and Chief of the Division of Endocrinology and Metabolism, Ohio State University College of Medicine, Columbus

*Functional uterine bleeding may occur in any age group but is more common during adolescence and the menopausal period. Diagnostic technic and management vary with the patient's age, parity and physical and pelvic findings. The author considers the condition from the aspects of etiology, diagnosis and medical and surgical treatment, including a brief discussion of various endocrine preparations that are effective in stopping abnormal menstrual bleeding and regulating abnormal cycles.*

# Dysfunctional Uterine Bleeding

WILLIAM C. KEETTEL*

*State University of Iowa College of Medicine, Iowa City*

FUNCTIONAL or dysfunctional uterine bleeding is irregular, excessive or prolonged menstrual bleeding caused by either endocrine or psychogenic factors. This definition excludes uterine bleeding associated with pregnancy, infection, tumors, malignant changes or systemic diseases. Dysfunctional bleeding can be said to exist only when all possible organic causes for irregular bleeding have been ruled out. Bleeding of this type is a common gynecologic symptom both in clinics and in private practice. Approximately 10 per cent of our new patients enter with this complaint. Since it is so common, it is proper for both the patient and her physician to place it in its proper perspective.

WILLIAM C. KEETTEL

### *Significance of Bleeding*

Figure 1, I think, depicts the dilemma that confronts the average physician in regard to the significance of irregular, excessive or prolonged menstrual bleeding. The woman on the left looks the picture of health but is telling the physician what a difficult time she has with menstruation. Her periods are most profuse, lasting many days and requiring many boxes of pads. She is nervous, tired and apprehensive and has lower abdominal discomfort. She may have dyspareunia and may say she cannot get along with her children or husband. On examination the physician finds normal pelvic organs and a normal hemoglobin. The patient on the right represents the opposite extreme, which is not uncommon. She looks chronically ill and apologetically tells the physician she feels a little tired and worn out but really hates to take up his time because she is not sure anything is wrong. She might admit that her periods have been a little excessive and prolonged but is sure this is unimportant. Her hemoglobin may be 3 to 6 gm., and one wonders how she has been able to perform her daily activities.

### *Organic Causes of Abnormal Uterine Bleeding*

Among the benign mechanical factors which may be responsible for abnormal uterine bleeding (figure 2), cervical polyp is a very frequent cause. Cervical erosion, while com-

*Professor of Obstetrics and Gynecology, State University of Iowa College of Medicine, Iowa City, Iowa.

Presented before the forty-third annual Assembly of the Interstate Postgraduate Medical Association at Cleveland.

FIGURE 1. Significance of vaginal bleeding.

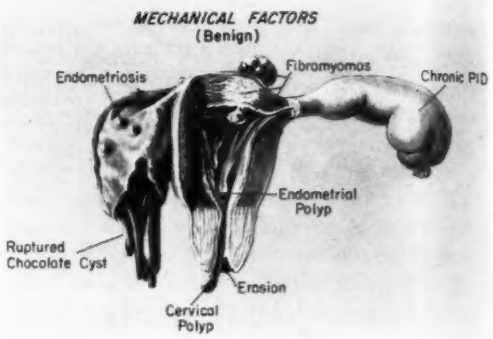



FIGURE 2.

mon, infrequently causes significant bleeding. Endometrial polyps are a common cause of menometrorrhagia. Many physicians believe that most fibromyomas produce irregular bleeding, but this is not the case. Only submucous myomas and intramural fibroids which encroach on the endometrial cavity are important in this respect. Subserous myoma, which is more common, does not produce abnormal menstruation.

Two conditions which can produce extensive ovarian damage and subsequent ovarian failure are chronic pelvic inflammatory disease and extensive bilateral ovarian endometriosis. One must always rule out malignant disease as a cause of abnormal bleeding (figure 3). The malignant changes responsible for such bleeding are cervical cancer, endometrial cancer, sarcoma and chorio-epithelioma, the first two being the more common.

Pregnancy factors also must be eliminated as a cause of abnormal bleeding (figure 4). These include incomplete abortion, hydatid mole and ectopic pregnancy. Chronic ectopic pregnancies often are associated with prolonged painful bleeding episodes and often are undiagnosed.

While it is rather uncommon for vaginal bleeding to result from defects of the hemopoietic system, these always should be considered. In our clinic we find four to six new cases of blood dyscrasias per year among patients sent to us because of serious anemia and associated uterine bleeding. The most common

FIGURE 3.

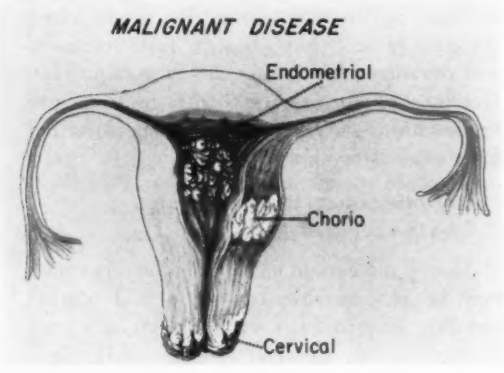
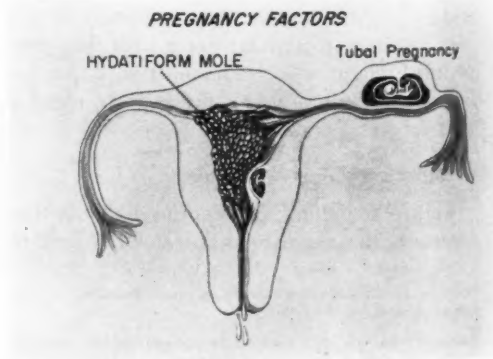



FIGURE 4.



types of blood dyscrasias associated with irregular vaginal bleeding are thrombopenic purpura, various forms of leukemia, and certain defects of coagulation. We feel that in every case in which the patient is severely anemic and there is a question concerning the amount of vaginal bleeding a careful investigation should be made to rule out a blood dyscrasia before a transfusion is given.

### *Endocrine Abnormalities*

Careful screening to eliminate organic factors leaves a group of patients with endocrine abnormalities as the causes of bleeding. In view of the complexities of the menstrual cycle and the various hormonal relationships responsible for normal menstruation it is a wonder that more abnormalities do not occur. The pituitary produces follicle-stimulating hormone, luteinizing hormone and the luteotropic hormones which stimulate follicular development, ovulation and corpus luteal activity in the ovary. The ovary in turn produces estrogen and progesterone to stimulate the proliferative and secretory changes of the endometrium. With menstruation a drop of hormonal levels occurs, with constriction of the spiral arteries and subsequent hemorrhage into the endometrium.

It is worthwhile to consider the endocrine changes responsible for abnormal uterine bleeding. Four defects are commonly mentioned: anovulatory cycles, low estrogen levels, defective or prolonged progesterone effect, and a vasomotor disturbance of the spiral arteries of the endometrium.

When estrogen is given cyclically, withdrawal bleeding occurs four to seven days later. Figure 5 shows anovulatory cycles with a sharp drop in estrogen levels and resultant regular withdrawal bleeding. If corpus luteal activity is maintained for a long period, irregular bleeding results which is called irregular shedding of the endometrium.

If estrogen levels are sustained over long periods, endometrial hyperplasia is produced and estrogen breakthrough bleeding occurs (figure 6). This is characterized by prolonged intermittent brownish discharge with episodes of profuse bleeding. Patients with low levels

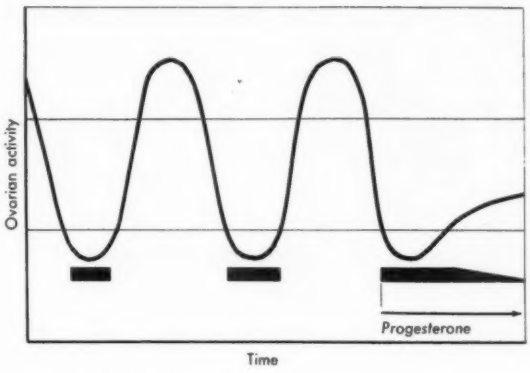
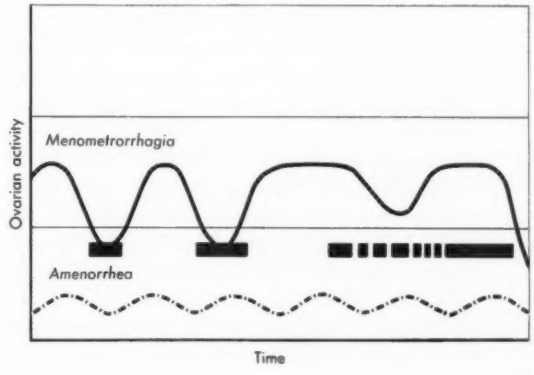



FIGURE 5. Anovulatory cycles. Solid line represents fluctuating production of estrogen.

of ovarian activity do not produce enough estrogen to stimulate the endometrium, and amenorrhea results. With partial ovarian failure enough estrogen may be produced to build up the endometrium but this is not sustained and irregular bleeding occurs.

Figure 7 illustrates the effect of aging on menstruation. With adolescence, ovarian activity gradually increases. Estrogen levels may fluctuate irregularly or may be sustained over long periods with no progesterone effect, and dysfunctional bleeding may result; but as the ovaries mature, hormonal relationships are established with ovulatory cycles and regular menstruation. Thus with time and patience such bleeding problems eventually are correct-

FIGURE 6. Prolonged estrogen effect. Wavy lines represent estrogen levels.



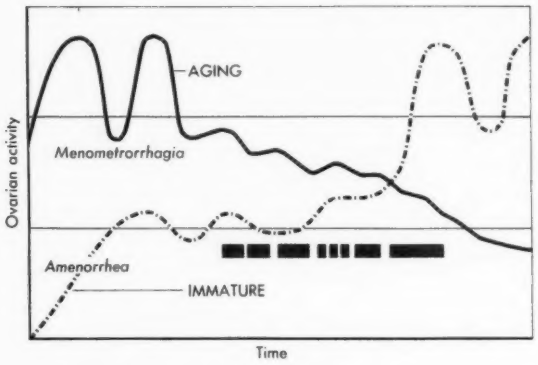



FIGURE 7. Effect of aging on ovarian activity.

ed. However, with the aging process the reverse is true. With beginning ovarian failure, menstrual irregularities occur due to estrogen breakthrough bleeding. At first only occasional periods may be abnormal, and later the majority may be abnormal. In complete ovarian failure, the periods cease and the patient becomes menopausal. This transition may extend over several years and be most trying to the patient.

### *Pertinent Clinical Facts*

Functional uterine bleeding is more common during the preclimacteric period, but it may occur at any time during the menstrual life of a woman and occasionally is encountered in adolescence; uterine bleeding in such cases is always painless. Dysfunctional bleeding often is preceded by a period of amenorrhea, particularly in the preclimacteric period. At first there is only spotting. Later there are episodes of profuse bleeding, followed by more spotting, and each day the patient expects and hopes the bleeding will stop. In other instances the bleeding starts as a regular period but is prolonged. Some patients have true menorrhagia characterized by excessive flow the first to third days of a period. Spontaneous remission is part of the natural history of this disorder, and the patient will revert back to normal menstruation for months or even years. Pelvic findings are normal. There are no characteristic changes in the uterus, tubes or ovaries. The position of the uterus is unimportant.

These patients bleed from a variety of endometrial patterns. While endometrial hyperplasia is the most common histologic picture, one may find proliferative endometrium, secretory endometrium and even atrophic endometrium. The hyperplastic-type endometrium that is found is not a precursor of an endometrial cancer. However, in certain patients there is a rare adenomatous type of hyperplasia which requires close observation.

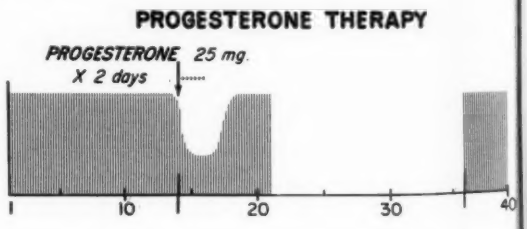
### *Steroid Preparations to Control Bleeding*

Since bleeding often is very profuse, it is necessary to stop this hemorrhage as promptly as possible. The oxytocic drugs and protamine have not been useful in our experience to control it.

*Progesterone*—With progesterone therapy, 25 mg. is administered intramuscularly on two successive days (figure 8). Bleeding diminishes for three or four days, and this is followed by rather profuse bleeding lasting another three or four days. Bleeding then stops for 26 to 30 days. This is the so-called chemical curettage which produces a complete sloughing of the endometrium. Some physicians like to repeat such therapy for several cycles, producing withdrawal bleeding by giving 50 mg. of progesterone on the twenty-sixth day of the cycle.

*Estrogen*—Estrogen is another effective steroid which can be used to stop menstruation (figure 9). Innumerable estrogenic preparations are available, and the question is often asked whether the naturally occurring estrogens are superior to the synthetic products. There is no difference, except in dosage. It is wise for the physician to become familiar with

FIGURE 8.



one type of estrogen and learn its use rather than shift from one to another. We are most familiar with an inexpensive estrogen, stilbestrol. To stop bleeding, 5 mg. of stilbestrol is given daily for two or three days. Usually within 24 to 48 hours the bleeding stops. Occasionally nausea may be a disadvantage. With cessation of bleeding the daily dose is decreased to 3 mg., and this dosage is continued for 20 days. Then administration of the steroid is stopped until withdrawal bleeding occurs.

PREMARIN® can be given orally or intravenously. Orally, between 30 and 50 mg. per day is required. Intravenously, 30 mg., which may be repeated, usually will stop the bleeding. Smaller amounts of estrogen must be continued to prevent withdrawal bleeding.

*Testosterone*—Testosterone is another hormone that can be used to control heavy menstruation (figure 10). We have had success with DELATESTRYL®, using 200 mg. per day for two days. If the total monthly dosage does not exceed 450 mg., virilizing effects are not noted. Testosterone has one advantage in that further therapy is not required and the period of amenorrhea may last 30 to 40 days.

*19 Nor-progestin compounds*—There are several of the 19 nor-progestin compounds on the market. ENOVID®, a progesteronelike compound combined with a low-potency estrogen, is an example. It can be administered orally, 10 to 30 mg. per day. Bleeding ceases within 12 to 48 hours (figure 11). Following cessation of bleeding, 10 mg. per day is given for 21 days, withdrawal bleeding occurring in four days. The endometrium shows a marked decidual effect. This medication is well tolerated except for mild nausea and occasional breast tenderness. It still is very expensive.

### *Philosophy of Management of Functional Uterine Bleeding*

Two very different approaches to the management of functional uterine bleeding, and their results, are depicted in figures 12, 13 and 14. On the left is a patient whose physician is very busy. Perhaps he performs a pelvic examination, but he does not inspect the cervix or carry out vaginal cytology. Immediately he gives hormones hypodermically with little explanation except that the cervix is "bad," the ovaries are diseased, and if the "shots" won't work everything must be removed or cancer may develop. When the patient leaves the doctor's office she is confused and frightened and seeks consolation and additional advice from her neighbors. She is told how bad she looks and how Mrs. X had just the same problem and now she is dead or has had a series of operations.

The majority of physicians will obtain a careful history and conduct a complete physical examination including pelvic examination, cervical inspection, vaginal cytology and the necessary laboratory tests. The patient who has had a careful and complete examination (shown on the right in figures 12, 13 and 14), and whose physician has discussed with her

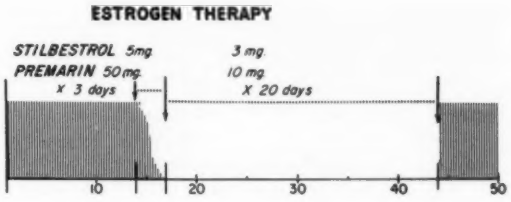



FIGURE 9.

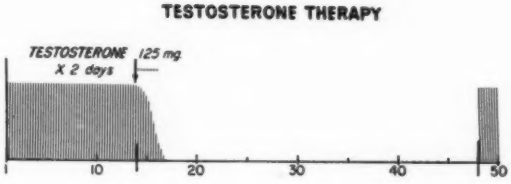



FIGURE 10.

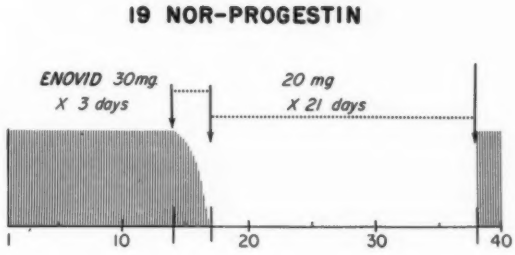



FIGURE 11.

FIGURES 12, 13 and 14. Management of functional uterine bleeding.

the significance of her problem, leaves his office satisfied that a complete evaluation has been made. She knows exactly what her problem is and can lead a very active, normal life, in contrast to the other patient, who is depressed, upset, and of little value to her family or the rest of society.

### *Treatment by Age Groups*

The following brief summaries of management of dysfunctional uterine bleeding by age groups emphasize some of the important aspects of treatment (table 1).

*Adolescents (11 to 21 years)*—It is wise to do a gentle pelvic examination even in this age group. With a small speculum the cervix may be visualized. In these patients the bleeding usually is due to inadequate progesterone effect, so progesterone is an ideal drug. It may take longer to control the bleeding cycles, and this should be explained carefully to the patient and her mother. After the bleeding has stopped one can produce cyclic bleeding by giving 50 mg. of progesterone on the twenty-fourth day of the cycle. Many of these girls have a deficiency of iron storage, and it is very important to build up iron reserves by continuous iron therapy over long periods of time. Patients with very low hemoglobin levels will benefit from blood transfusions. We feel that a patient whose hemoglobin is 8.5 gm. or less or whose hematocrit is 26 per cent or less should be transfused. Thyroid therapy used to be a popular adjunct to control bleeding problems. With the advent of more precise methods of determining thyroidal function, hypothyroidism is rarely encountered. Dilatation and curettage are rarely necessary. Usually one can control the bleeding until the ovaries mature and regular cyclic menstruation occurs. Hysterectomy is never required in this age group. It is surprising how many patients can be cured of irregular bleeding by having them keep accurate menstrual records.

*Young women (21 to 35 years)*—In this age group one must rule out pregnancy factors and malignant disease. Many patients should be treated by primary dilatation and curettage. This is of value for both diagnosis and therapy; in more than 50 per cent of the cases the procedure will control the bleeding problem. In certain cases one may elect to obtain an endometrial biopsy and try hormonal management where malignancy need not be considered. Here testosterone, Enovid or estrogens can be used to stop the bleeding, followed by artificial cycles with estrogen or Enovid. If

TABLE 1

MANAGEMENT OF DYSFUNCTIONAL UTERINE BLEEDING IN THE VARIOUS AGE GROUPS

*Adolescents (11 to 21 years):*

1. Progesterone to stop and regulate flow
2. Iron therapy or blood transfusions
3. Thyroid therapy
4. Dilatation and curettage rarely needed
5. Hysterectomy never required

*Young women (21 to 35 years):*

1. Dilatation and curettage, testosterone or Enovid to stop bleeding
2. Artificial cycle with estrogen or Enovid
3. Treatment of anemia
4. Hysterectomy for recurrent bleeding

*Preclimacteric group (35 to 50 years):*

1. Always perform dilatation and curettage first to rule out malignancy
2. Endocrine therapy not as effective
3. Treatment of anemia
4. Hysterectomy with ovarian conservation for patients with marked anemia or recurrent bleeding
5. Irradiation castration for obese or poor-risk patients

the patient is anemic, iron therapy or blood transfusion should be utilized. Certain patients who have recurrent episodes of vaginal bleeding and anemia following conservative management (hormones and dilatation and curettage) extending over a year are best treated definitively when childbearing is not of importance. Depending on anatomic findings, abdominal total hysterectomy or vaginal hysterectomy is done.

*Preclimacteric group (35 to 50 years)*—Dilatation and curettage always should be done initially to rule out malignancy. The physician who starts with endocrine therapy in this age group without eliminating malignancy is open to criticism. Endocrine therapy is not as effectual in this group, but cyclic progesterone therapy may give good results. Since childbearing is not of major importance, physicians are more prone to use definitive therapy, but this is unwise until conservative management has failed. Conservative management should consist of at least one or perhaps two curettages and some form of endocrine therapy for six months to a year. Today hysterectomy is the best method of management of a severe bleeding problem which has not responded to conservative therapy. Either an abdominal total hysterectomy or a vaginal hysterectomy with ovarian conservation can be done. In the past, intracavitary radium or x-ray to eliminate ovarian function was a useful method, but today it is no longer recommended for two reasons: recurrent uterine bleeding and the possibility of development of malignancy. X-ray castration still is useful in certain cases of very obese women or poor-risk patients who require definitive therapy.

### *Conclusions*

1. One must be sure there is a definite bleeding problem.

2. Organic causes, particularly malignancy, must be ruled out by complete examination including physical and pelvic examinations, cytology and the necessary laboratory tests.

3. One must be familiar with the various endocrine factors responsible for abnormal uterine bleeding.

4. Certain steroid preparations, if properly used, are fairly effective in stopping and controlling bleeding.

5. Dilatation and curettage are the most effective means of control and diagnosis.

6. Conservative treatment should be used in adolescent patients.

7. In the preclimacteric group definitive treatment should be employed when there has been failure of conservative therapy with severe recurrent bleeding.

*Antral gastritis rarely should be considered a primary lesion. It often is due to antral irritability secondary to peptic ulcer or carcinoma. Four case reports illustrate the dangers of accepting a diagnosis of antral gastritis without further investigation. Close observation and re-examination often will reveal the underlying cause of antral abnormalities.*

# What Is Antral Gastritis?

JOHN M. WEBER* AND R. DOUGLAS DOSS†

*Veterans Administration Hospital, Pittsburgh*

THE term antral gastritis is widely used in medical literature, and it often is seen in roentgenologic reports. To many physicians, it implies a benign hypertrophic gastritis limited to the antral segment of the stomach. It is the purpose of this communication to emphasize that this diagnosis carries a serious implication because of the underlying disease that frequently is present. In this paper, the term antrum will be used to designate that segment of the stomach bounded cephalically by the angulus and musculus sphincter antri and distally by the pyloric canal.[1] The term gastritis will be used to designate a coarsening, thickening or distortion of the gastric mucosa visualized roentgenographically.

Ritvo and Shauffer[2] said that antral gastritis may closely resemble an infiltrating carcinoma in cases in which there is considerable thickening of the antral mucosa. According to these authors, bleeding occurred in 12 per cent of a group of reported cases of supposedly uncomplicated antral gastritis.

*Chief of Gastroenterology, Veterans Administration Hospital, and Instructor in Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

†Assistant Chief of Radiology, Veterans Administration Hospital, Pittsburgh, Pennsylvania.

JOHN M. WEBER

R. DOUGLAS DOSS

Our observations and conclusions are based on 2000 roentgenologic examinations of the upper part of the gastrointestinal tract that were made by one of us (R.D.D.) and 1500 gastroscopic examinations that were made by the other (J.M.W.). We shall report four illustrative cases in which the primary roentgenologic diagnosis was antral gastritis.

### *Case Reports*

*Case 1*—A 48 year old white man was first admitted to the Veterans Administration Hospital in Pittsburgh in May 1950. He had had severe, persistent epigastric pain for three months, and he had lost 15 lb. He had vomited occasionally, but there had not been any

bleeding. The value for the free hydrochloric acid in the fasting gastric contents was 37 units. Roentgenologic examination revealed only antral gastritis (figure 1). This diagnosis was based primarily on distortion of the antral mucosa and rather marked irritability of the antral portion of the stomach. The patient responded to treatment with a bland diet, mild sedation and antispasmodics.

He was readmitted to the hospital in November 1950. At that time, his symptoms were similar to those that had been present at the time of his previous admission, and the roentgenologic findings were the same as they had been previously. Gastroscopy revealed antral irritability, but it did not disclose any gross evidence of gastritis or an ulcer. The lesser curvature and posterior wall of the antrum were not seen when gastroscopy was performed. The patient again responded to a simple therapeutic regimen, and he was dismissed from the hospital.

He was admitted to the hospital for the third time in August 1951. An exploratory laparotomy was performed because of the severity of the symptoms and the continued loss of weight. A chronic benign gastric ulcer, 3 cm. in diameter, was found on the posterior wall of the antrum, and a subtotal gastrectomy was performed. When last observed, the patient had been free of symptoms for one year after the operation.

In this case, there was an 18 month history of recurrent epigastric pain. On three occasions, roentgenologic examination revealed distortion and irritability of the antrum, but did not disclose an ulcer. These roentgenologic findings are commonly accepted as being characteristic of antral gastritis. The extreme irritability of the antrum caused distortion of the mucosa and prevented the demonstration of a niche. When the patient's symptoms became severe enough to warrant an exploratory laparotomy, a previously unidentified chronic gastric ulcer was found.

*Case 2*—A 76 year old Spanish-American War veteran was admitted to the hospital in October 1949 because of diarrhea and mild dyspepsia. There was no history of loss of weight or vomiting, and his appetite was good.

FIGURE 1. Distortion of the antral mucosa in case 1.

The results of routine laboratory tests were within normal limits. On two previous occasions, the patient had been admitted to the hospital because of diarrhea, which had recurred intermittently for 50 years after a severe attack of dysentery which had occurred in the Philippines in 1898.

Examination of the stools, roentgenographic examination of the colon with a barium enema, and proctoscopy did not disclose any abnormality. Roentgenologic examination of the upper part of the gastrointestinal tract revealed minimal coarsening of the antral mucosa consistent with so-called antral gastritis (figure 2). Symptomatic and empirical treatment for amebiasis caused the diarrhea to subside, and the patient was dismissed. When he returned to the hospital one year later, he had an inoperable carcinoma of the distal portion of the stomach (figure 3).

In this case, a diagnosis of antral gastritis

FIGURE 2. Minimal coarsening of the antral mucosa in case 2.

FIGURE 3. Inoperable carcinoma of distal portion of stomach in case 2.

lulled the clinician into a false sense of security. It is possible that earlier recognition of the fact that antral gastritis rarely should be considered a primary lesion might have saved the life of this patient.

*Case 3*—A 64 year old Negro was admitted to the hospital in May 1952 because of mild dyspepsia and slight loss of weight. The results of roentgenologic examination of the upper part of the gastrointestinal tract were interpreted as normal. Although gastroscopy permitted a good view of the antrum and visualization of the peristaltic waves, it did not reveal any abnormality. A simple therapeutic regimen relieved the symptoms, and the patient was dismissed.

When he returned one year later, he had an obstructing carcinoma in the prepyloric region. In retrospect, the initial roentgenograms of the upper part of the gastrointestinal tract revealed a minimal irregularity in the antrum, which is consistent with so-called antral gastritis. This was another case in which minimal changes in the antrum were overlooked. It also illustrates the fallibility of gastroscopy in cases in which lesions are situated close to the pylorus.

*Case 4*—A 61 year old Negro was admitted to the hospital in October 1957. He had had epigastric pain for a short time, and he had lost 25 lb. Laboratory tests showed mild anemia. Free hydrochloric acid was found in the fasting gastric contents. On two occasions, roentgenologic examination disclosed distortion and narrowing of the antrum, which are consistent with antral gastritis. Gastroscopy was not satisfactory.

Improvement occurred, and the patient gained 8 lb. However, because the presence of a carcinoma was suspected, an exploratory laparotomy was performed. Hypotension developed shortly after the abdomen was opened, and the operation had to be terminated. Before the abdomen was closed, the surgeon was able to palpate the portion of the antrum which was believed to be the site of the carcinoma, but he could not detect any abnormality. When a third roentgenologic examination revealed a persistence of the antral changes, another exploratory laparotomy was performed. On this occasion, it disclosed a chronic, benign antral ulcer.

In this case, antral distortion, which was detected by roentgenologic examination on three occasions, was discovered to be due

to a chronic gastric ulcer when an exploratory laparotomy was performed. Even palpation failed to reveal the ulcer at the time of the first exploratory operation.

### *Comment*

The cases that we have reported illustrate the dangers of accepting a diagnosis of antral gastritis at its face value. One of us (J.M.W.) has performed more than 1500 gastroscopic examinations and has found gross evidence of antral gastritis only in cases in which marked organic pyloric stenosis was associated with retention or in cases of a submucosal, infiltrating new growth. It is our opinion that distortion of the antral mucosa leading to a diagnosis of antral gastritis is often due to antral irritability secondary to a peptic ulcer or to an infiltrating malignant lesion. In the former case, barium is prevented from clinging to the mucosa, and this makes the demonstration of a niche most difficult. The situation is analogous to the Stierlin sign in cases of cecal tuberculosis.[1]

Antral carcinoma that resembles antral gastritis is an even more serious problem. The roentgenologist who detects a minimal or inconstant abnormality in the antrum may be reluctant to venture a suspicion of carcinoma on such meager evidence. The term antral gastritis, now accepted generally, has been applied to slight abnormalities of this type. If simple therapeutic measures produce improvement in a case in which a diagnosis of antral gastritis has been made, the clinician gains a false sense of security. Such improvement occurred in two of the cases which we have reported. In both of these cases, the patients subsequently returned with an inoperable carcinoma. Gastroscopy is not reliable in such cases, because the lesions may be largely submucosal, or they may be too close to the pylorus to permit the gastroscopist to express a reliable opinion.

Walters, Gray and Priestley[3] have shown the importance of the antral area in cases of gastric carcinoma. According to these authors, the lesion was situated in the midportion or in the pyloric end of the stomach in more than 80 per cent of approximately 2000 cases of carcinoma of the stomach in which the patients survived operation.

It is not our purpose to suggest the abandonment of the term antral gastritis. It is clear, however, that this term must be used guardedly and that the roentgenologist and clinician should be hesitant to use it to designate a primary lesion. The use of the term may be acceptable if all parties concerned realize that it is used to describe some antral abnormality, the nature of which is not precisely clear. Close observation and re-examination of the patient will often reveal the underlying disease causing the antral changes.

These antral changes usually are secondary to scarring or adhesions due to a previous ulcer, to antral irritability caused by an active ulcer either in the antrum itself or in the duodenum, or to an early infiltrating carcinoma. If these possibilities are kept clearly in mind by the roentgenologist and clinician when the diagnosis of antral gastritis is made, the correct management of the patient will be clear.

### *Summary*

Antral abnormalities loosely designated as antral gastritis are commonly secondary to other antral disease, either ulcer or carcinoma. Patients with antral abnormalities should be followed closely both roentgenologically and clinically.

### REFERENCES

1. Bockus, H. L.: Gastro-enterology. Philadelphia, W. B. Saunders Company, 1943-1944, vol. 1, page 171, and vol. 2, p. 203.
2. Ritvo, M. and Shauffer, I. A.: Gastrointestinal X-ray Diagnosis. Philadelphia, Lea & Febiger, 1952, p. 175.
3. Walters, W., Gray, H. K. and Priestley, J. T.: Carcinoma and Other Malignant Lesions of the Stomach. Philadelphia, W. B. Saunders Company, 1942, p. 506.



UNIVERSITY OF MICHIGAN LIBRARIES

# Medical Evaluation of the Patient Before Operation

LLOYD S. RALSTON*

*University of North Dakota School of Medicine, Grand Forks*

*Evaluation of the patient about to undergo operation is a responsibility the surgeon often wishes to share with the internist. Careful and critical appraisal is of inestimable value in accomplishing the primary objective—a living patient who has been benefited by his operation. This paper reviews some of the problems, foreknowledge of which will help toward that objective.*

LLOYD S. RALSTON

THE widely developing field of medicine stands in sharp contrast to the apparently narrowing field of an individual specialist's activity. This has been a source of much debate and reflection. Practically, it has many implications. The evaluation of a patient for a surgical procedure may require the cooperation of an internist. Although the conscientious surgeon always will make a careful examination, he often will request the opinion of other skilled colleagues.

When a surgeon requests a preoperative evaluation of a patient by an internist, he probably wants to know: (1) the percentile chance that the patient will be able to withstand the operation, and (2) what may be done preoperatively, operatively and postoperatively to maintain or increase the patient's chance of survival. To a lesser extent, the surgeon perhaps will want to know: (1) whether an operation is necessary, and (2) whether the prognosis of a possibly associated disease is so good that the patient may have a reasonable chance of surviving long enough to enjoy the benefits of the operation.

This paper is not intended to consider more complicated procedures that require team action, such as the evaluation of a patient for a cardiac operation or the estimation of pulmonary function in a case in which an operation is to be performed on the lung. The aim is to consider the evaluation of the patient for a "run of the mill" surgical procedure. If the examination is to furnish the surgeon all of the desired information, it will require considerable time. Little objective evidence is

*Assistant Professor of Clinical Medicine, University of North Dakota School of Medicine, and the Grand Forks Clinic, Grand Forks, North Dakota.

available concerning the actual strain imposed by a surgical operation. Therefore, one must depend on experience to a great extent.

### *Apprehension and Other Psychologic Factors*

Apprehension sometimes is detected by the internist, and it sometimes is expressed by the patient during an interview. It occasionally occurs because the patient has inadequate knowledge of what is happening to him or of what is to be done. Careful discussion sometimes will relieve the apprehension, and it certainly will influence the preoperative medication. A patient who is very apprehensive is a potential candidate for operative death or difficulty.[1]

Psychologic factors other than apprehension may be so varied as to confuse the internist and the surgeon. A patient's emotional investment in the organ system to be operated on may be a contributing factor. Postoperative psychosis is most often observed after operations on the eyes and genitalia. The best prophylaxis is careful attention to the patient's need to know what is happening to him.

### *Age*

In determining operability, even in cases in which the patients are poor operative risks, chronologic age probably is less important than associated disease states. There would seem to be general agreement that chronologic age often is a poor indication of the physiologic age of tissues.[2] Actually, age alone very seldom is a contraindication to operation. However, this statement must be qualified by a recent report[3] in which the author said that the following cardiovascular changes are likely to be present in aged persons: (1) a decrease in the cardiac output, (2) an increase in the size of the heart, (3) a prolongation of systole, (4) an increase in the systolic pressure, (5) an elevation of the total vascular resistance, and (6) a decrease in tissue and cellular perfusion.

Perhaps the borderline reserve that possibly is present in persons who appear to be completely healthy eventually will be demonstrated to be present in many physiologic systems of aged persons. Frequently, the most careful evaluation with readily available diagnostic procedures, such as electrocardiography and roentgenography, may reveal little or no evidence of cardiovascular or other disease.[2] The internist, therefore, must look for subtle suggestions of dysfunction, such as shortness of breath that occurs when the patient walks into the wind and coughing that occurs as a result of exertion. As a result of these findings, the internist may wish to suggest the administration of digitalis or another drug in order to prevent the occurrence of an unexpected cardiovascular complication.

In cases in which there is evidence of arteriosclerotic disease of the brain, extension of the disease may occur after an operation.[2] This complication perhaps has not been emphasized sufficiently. This extension of the disease may result in cerebral thrombosis. For this reason, evidence of arteriosclerotic disease of the brain may be a relative contraindication to operation, but if an operation is performed, particular care should be taken to prevent development of cerebral thrombosis.

### *History of Preoperative Administration of Drugs*

The patient may have been taking one or more of the newer drugs such as adrenocortical hormone, *Rauwolfia* derivatives and chlorpromazine for several months before operation. The use of these products introduces a relatively unfamiliar hazard, because they seem to affect the circulation when the patient is subjected to anesthesia and operation. The mechanism of this action may not be well understood, but the danger is real.

If the patient has been taking adrenocortical hormone up to the time of the operation or in the recent past, its administration should be continued carefully or larger doses should be administered during the period of surgical treatment. To deprive the patient of this drug, even unwittingly, may leave him with unreactive or exhausted adrenal glands and inability to respond well to surgical stress.[1]

The effects of the *Rauwolfia* derivatives persist for about 10 days after the administration of these drugs is discontinued. Prolonged



UNIVERSITY OF MICHIGAN LIBRARIES

use of these drugs prior to operation may cause severe hypotension at the time of operation.[4] The hypotension may occur at any time after the induction of anesthesia is started, and it may persist for several days after the operation. The cause of this hypotension is not well known. Prolonged intravenous administration of vasopressor agents and other supportive drugs may be required to relieve the hypotension.

It can easily be proved that chlorpromazine causes hypotension, especially during anesthesia. This often occurs when the patient is tilted after the induction of anesthesia. This action apparently is due to loss of reflex circulatory control.[1]

It is important to determine whether mercurial diuretics have been administered, because electrolyte imbalance may occur in cases in which these drugs have been administered for a long time.

A history of the administration of digitalis implies the presence of cardiovascular disease. Furthermore, digitalis toxicity may become a clinical problem if hypokalemia develops during the postoperative period. The use of quinidine also may imply the presence of cardiovascular disease. This drug may produce complications if curare is administered at the time of operation.

Careful inquiry should be made regarding the preoperative use of antibiotics, because the widespread use of these drugs has caused sensitization in some cases. Little need be said about the importance of determining whether suppressive treatment for epilepsy has been used before the operation.

I have considered only a few of the drugs that may have been used before operation. It is extremely important to inquire about the drug habits of patients who are to undergo an operation.

### *Problems Referable to the Heart*

I believe that the following diseases of the heart should be considered strong contraindications to a major operation: (1) acute myocardial infarction occurring within three months before the operation, (2) congestive heart-failure, (3) uncontrolled cardiac arrhythmia, (4) active myocarditis, (5) pericarditis, (6) subacute bacterial endocarditis.

The surgical risk is greatly increased if the operation is performed after a recent myocardial infarction. This is one reason why the internist may wish to make an electrocardiogram before the operation. If possible, the operation should be delayed if myocardial infarction has occurred within three months. This is the time generally accepted as being necessary for satisfactory healing. If the history reveals angina of increasing severity or its occurrence as a result of progressively less exertion, one might well suspect impending coronary occlusion and recommend delay or avoidance of the operation. It is well to keep in mind that the incidence of cardiorespiratory complications, fresh infarction, bronchopneumonia, pulmonary embolism and congestive heart-failure is high in cases in which myocardial infarction has occurred previously. This statement also applies to marked cardiomegaly and previous or present instances of heart-failure.

Some types of uncontrolled arrhythmia are far more important than others. For instance, uncontrolled atrial flutter and atrial fibrillation increase the operative risk because the pulse rate may increase precipitously during operation and result in congestive heart-failure or myocardial infarction.[2] The patient should be observed for the possible presence of auricular or nodal tachycardia. If either of these conditions is present, it should be treated. Premature auricular or ventricular contractions may forewarn of incipient cardiac failure or that a more serious type of arrhythmia may develop at the time of the operation. If an uncontrolled arrhythmia is present, one is justified in asking the surgeon to postpone the operation while an attempt is made to control the arrhythmia.

Active myocarditis, pericarditis and subacute bacterial endocarditis probably do not require further consideration. One may say, however, that it is extremely important to determine whether any of these diseases is present, and to institute treatment before operation is performed.

There are certain other cardiac problems

that can be listed as operative hazards because they predispose to the development of arrhythmia or shock associated with cardiac dilatation, pulmonary edema, fresh infarction, phlebitis and embolism at the time of operation. These problems include: (1) coronary disease and angina, (2) marked cardiac enlargement, (3) heart block and Stokes-Adams syndrome, (4) chronic cor pulmonale, and (5) paroxysmal nocturnal dyspnea.[2]

From the medical point of view, angina and coronary artery disease probably are the leading causes of unexpected disaster in the operating room.[1] One, therefore, should be certain that the indications for the operation are unequivocal in cases in which this disease is present. If the indications for the operation are unequivocal, intelligent management will save a great majority of the patients. The internist must apprise the surgeon of the risk in order that greater care can be exercised relative to hypoxia, hypotension, circulatory overload, the prevention of preoperative tension and anxiety, and the avoidance of deep anesthesia if possible. Knowledge of the presence of this condition will give the surgeon a better chance to prepare the patient's family for a possible disaster.

Marked cardiomegaly is one of the mechanisms available to the heart in its attempt to compensate for disease. In order to maintain this compensation, the coronary vessels must supply increased amounts of oxygen and nutriment. Surgical hemorrhage is a threat to this nutrition of the heart muscle, and the loss of small amounts of blood that normally would be well tolerated may result in serious or fatal myocardial damage in cases in which marked cardiomegaly is present. In addition, hemorrhage may result in hypotension and may further decrease perfusion in a large heart that has difficulty in maintaining its blood supply under normal conditions. If cardiomegaly is present, the overzealous administration of fluids or blood by the parenteral route during or after operation may precipitate congestive heart-failure.

One evidently must distinguish between the presence or absence of attacks of Stokes-Adams syndrome in cases of heart block. It is well known that sudden cardiac arrest is likely to occur in cases of Stokes-Adams syndrome. The stress associated with operation and anesthesia evidently increases the risk of sudden cardiac arrest in these cases. Heart block without attacks of Stokes-Adams syndrome poses less of a problem. Most authors recommend that patients with Stokes-Adams syndrome should be routinely digitalized before operation, regardless of whether or not cardiac failure is present, and that effective doses of atropine sulfate and ephedrine sulfate should be administered every four to six hours.[2]

Chronic cor pulmonale develops as a result of long-standing pulmonary disease. Time should be taken to make the diagnosis. After the diagnosis has been made, all infection should be controlled, phlebectomy should be performed if the hematocrit reading is higher than 53 per cent, the patient should be digitalized, and oxygen should be administered judiciously. When oxygen is used, one should consider the possibility of oxygen toxicity.

Patients with paroxysmal nocturnal dyspnea often consult a physician because they are having nocturnal attacks of "asthma," and only close questioning will reveal that they are having attacks of paroxysmal nocturnal dyspnea. In many cases, this condition is associated with hypertension. Treatment should include rest in bed and the administration of digitalis and diuretics. Intensive antihypertensive therapy may be necessary. A low salt diet should be used to achieve "dry" weight before operation is performed.

The following cardiac conditions are of less importance to the surgeon than those that have been considered previously: (1) bundle-branch block, (2) healed myocardial infarction, (3) heart block without attacks of Stokes-Adams syndrome, (4) controlled auricular fibrillation, (5) aortic valvular disease, and (6) aortic aneurysm.

Bundle-branch block per se probably is not a major contraindication to operation,[5] but it must be evaluated on the basis of a possible underlying disease of the heart. One survey has shown that postoperative shock is more frequent in patients who have bundle-branch block.

Healed myocardial infarction[6,7] per se likewise is not a contraindication to operation. However, postoperative cardiorespiratory complications are prone to occur in cases of healed myocardial infarction. Long surgical procedures and the use of PENTOTHAL® sodium anesthesia evidently increase the risk of the development of these complications.

A decrease in the blood pressure is very likely to occur during operation in cases of aortic valvular disease. The decrease in the mean aortic pressure may be sufficient to precipitate coronary occlusion or renal failure.

Aortic aneurysm, of course, implies the presence of cardiovascular disease. Knowledge of the presence of an aortic aneurysm is of value to the surgeon when surgical procedures involving manipulation of the mediastinum are contemplated.

Infection is more prone to occur in patients with cardiac disease than in other patients, and it is more likely to prove fatal. Antibiotic therapy has greatly reduced this danger.

Postoperative thrombo-embolic disease also is more prone to occur in patients with cardiac disease,[8] and it is more likely to prove fatal. The surgeon, therefore, should take special care to prevent this complication.

Operation may be mandatory in the presence of some other conditions, regardless of the cardiac status, or at least before a completely optimal cardiac state can be obtained. The following conditions may be included in this category: (1) acute massive hemorrhage, (2) perforation of a viscus, (3) acute cardiac tamponade, (4) strangulated hernia, (5) acute phlegmonous appendicitis, (6) ovarian cyst with a twisted pedicle, (7) mechanical obstruction of the intestine, (8) acute gangrenous or suppurative cholecystitis, and (9) peripheral embolism.[9]

### *Problems Referable to the Respiratory Tract*

Pulmonary emphysema, which most commonly is observed in elderly persons, makes the administration of a general anesthetic difficult because of poor gaseous exchange and an increase in secretions. After operation, the patients have trouble in clearing the respiratory tract of secretions. The result is an increased incidence of atelectasis and postoperative pneumonitis. The patient may die after operation because an inability to keep the respiratory tract clear of secretions precludes adequate ventilation.[1]

The anesthetic complications are of paramount importance in cases of bronchial asthma. The use of Pentothal sodium, cyclopropane and morphine sulfate is contraindicated because of the possibility that they may induce bronchospasm.[1] The bronchospasm may be merely a frightening episode, or it may cause death. It is doubtful whether Pentothal sodium ever should be used in a case in which there is a history of bronchial asthma.

### *Problems Referable to the Endocrine Glands*

Diabetes is an obvious endocrine problem, and it certainly should be detected and controlled before operation. Even if it is controlled, the surgical risk may be somewhat increased due to associated vascular disease.

Operation is tolerated poorly in cases of uncontrolled hyperthyroidism, and cardiovascular complications or a thyroid crisis is likely to develop. Operation should be delayed until the hyperthyroidism can be controlled. Uncontrolled hypothyroidism is a contraindication to a major operation because vascular collapse often occurs during anesthesia, and cardiovascular complications are more likely to develop.

Adrenal or pituitary deficiency likewise is a warning sign. The presence of deficiency of either of these glands should be suspected if the patient is sensitive to cold, if the blood pressure is low, if the eosinophil count is high, and if the value for the serum electrolytes is abnormal. Replacement therapy is abundantly available.

### *Problems Referable to the Liver*

Hepatic disease such as active hepatitis or other types of marked hepatic dysfunction certainly adds to the hazard of a major operation. If the clinical findings suggest the presence of hepatic dysfunction, one might wish to confirm the diagnosis by determining the val-

ues for the total protein and the serum bilirubin, and by performing a BROMSULPHALEIN® test or a flocculation test. A stubborn prothrombin deficiency that cannot be corrected by the administration of vitamin K further increases the surgical risk.

### *Problems Referable to the Kidneys*

In cases of renal disease, the surgical risk is directly proportional to the decrease in renal function. If the specific gravity of the urine is consistently low, or if an increase in the value for the blood urea nitrogen can be explained on the basis of renal disease, other tests of renal function may be indicated. If a phenolsulfonphthalein test reveals an excretion of less than 20 per cent of the dye in one hour, or if a urea clearance test reveals marked impairment of the clearance of urea (30 per cent), or if a creatinine clearance test reveals a clearance of less than 40 per cent, it is an indication of severe renal damage. In cases in which any of these findings are obtained, the operative morbidity and mortality are increased.

Major operations are not tolerated well in cases of acute glomerulonephritis or the nephrotic syndrome. The most common cause of death in these cases is irreversible postoperative oliguria. Renal dysfunction caused by dehydration, hemorrhage, shock, fluid and electrolyte imbalance, and reduced blood volume usually is reversible with proper therapy. This emphasizes the necessity of distinguishing extrarenal azotemia from true renal disease.

### *Problems Referable to the Blood*

Some patients may have a diminished blood volume at the time of operation. This condition is most often observed in patients with carcinoma or ulceration of the intestine, in debilitated persons, and in persons who have been confined to bed for a long time. Hypovolemia likewise may be present in sedentary elderly persons, in persons who have lost fluid as a result of extensive vomiting, diarrhea or hemorrhage, and in persons who previously have undergone multiple operations.[1] As a result of the stress of an extensive operation, the patient with hypovolemia may be unable to compensate for the effects of anesthetic depression, for changes in body position, or for additional loss of blood. The result may be an alarming hypotension resulting from what appears to be a minimal cause. An attempt should be made to correct the deficit in blood volume before operation is performed. I have found that a bleeding tendency is best detected by a carefully taken history. If the history suggests the presence of such a tendency, more elaborate investigation may be rewarding.

### *Conclusions*

Regardless of any physical complication that may exist, no patient should be denied an operation that will save his life or that will prolong his life, provided careful study and judgment indicate that there is a reasonable chance that he will survive long enough to enjoy the benefits of the operation. The internist, therefore, must take time to study the patient for major and minor indications of disease that may have a great bearing on the outcome of the operation.

REFERENCES


1. ECKENHOFF, J. E.: Some preoperative warnings of potential operating-room deaths. New England J. Med. 255:1075 (December 6) 1956.
2. LADUE, J. S.: Evaluation and preparation of the patient with degenerative cardiovascular disease for major surgery. Bull. New York Acad. Med. 32:418 (June) 1956.
3. LANDOWNE, M., BRANDFONBRENER, M. and SHOCK, N. W.: Relation of age to certain measures of performance of the heart and the circulation. Circulation 12:567 (October) 1955.
4. COAKLEY, C. S., ALPERT, S. and BOLING, J. S.: Circulatory responses during anesthesia of patients on Rauwolfia therapy. J.A.M.A. 161:1143, 1956.
5. PFEIFFER, P. H. and LADUE, J. S.: Major surgical operations in the presence of bundle-branch block; study of the operative risk in 59 patients. Am. J. M. Sc. 217:369 (April) 1949.
6. HANNIGAN, C. A., WRÓBLEWSKI, F., LEWIS, W. H., JR. and LADUE, J. S.: Major surgery in patients with healed myocardial infarction. Am. J. M. Sc. 222:628 (December) 1951.
7. WRÓBLEWSKI, F. and LADUE, J. S.: Myocardial infarction as a postoperative complication of major surgery. J.A.M.A. 150:1212 (November 22) 1952.
8. OCHSNER, A., DEBAKEY, M., DECAMP, P. T. and DA ROCHA, E.: Thrombo-embolism; analysis of cases at the Charity Hospital in New Orleans over a 12-year period. Ann. Surg. 134:405 (September) 1951.
9. FRIEDBERG, C. K.: Diseases of the Heart. Ed. 2. Philadelphia, W. B. Saunders Company, 1956, p. 1100.

# Some Problems in Anesthesia for Accident Victims

KARL L. SIEBECKER*

*University of Wisconsin Medical School, Madison*

KARL L. SIEBECKER

*Despite time limitations, accident victims must be given some preanesthetic evaluation before surgery. The condition of the circulatory system is probably of greatest importance. Preanesthetic medication should be minimal. The stomach must be evacuated. The patient's safety determines the choice of anesthetic. Respiration must be adequately maintained before and during anesthetization.*

PATIENTS scheduled for operation at least a day in advance are usually evaluated for general physical condition and for anesthetic and surgical risks. In the case of an accident victim, this sort of careful examination is rarely possible; he must, however, be given some preanesthetic evaluation, since he may be far from home and his family physician. Even if only a few minutes are available, a serious effort should be made to learn something about the patient and to improve his general condition before anesthesia is administered. Most specific injuries can be treated after proper blood replacement and after this evaluation. A properly reduced compound fracture in a dead body offers no comfort to the patient, his family, the anesthetist or the surgeon.

*Associate Professor of Anesthesiology, University of Wisconsin Medical School, Madison, Wisconsin.

### *Evaluation of Patient*

*Circulatory system*—Although the condition of the respiratory system is highly important, particularly in the administration of the anesthetic, the condition of the circulatory system, while more difficult to ascertain, is probably even more important. It is circulatory failure that will kill most of your patients. This is not said facetiously, and I do not refer to the old cliché that the heart must stop before the patient dies, whatever the immediate cause of death. I refer to shock or potential

shock. While not always obvious, potential shock should be suspected and prepared for in caring for any injured person. Obvious blood loss is not always a prerequisite for shock, since crushing injuries, pain, undiagnosed internal bleeding, and the condition of the patient before the accident all may contribute to potential circulatory failure. An apparently normal blood pressure level may be misleading, for the body may have used up all its reserve compensatory mechanism to make the heart and circulation *appear* normal. Excessive preanesthetic medication or the onset of anesthesia may precipitate circulatory failure.

*Respiratory system*—The condition of the respiratory system may, of course, affect the administration of the anesthetic, since maintenance of a free airway is absolutely necessary. If medical students are taught to recognize the necessity for a clear airway and to maintain one, they will save many lives, no matter what branch of medicine they enter.

Injuries to the head and neck may complicate the maintenance of a free airway. Endotracheal intubation, preferably with a cuffed tube, is a virtual necessity. However, even this procedure will not guarantee a clear airway, since kinking of the tube or accumulation of blood, secretions or vomitus may occlude the lumen.[1] The distal opening of the tube may rest against the tracheal wall, or the tube, if too long, may enter one bronchus. An endotracheal tube with a hole in each side is preferable because it will usually have at least one free opening. An endotracheal cuff should be inserted only 1 cm. past the glottis. Several types of apparatus, adaptable to many situations, allow the anesthesiologist to get out of the surgeon's way. Among these are the Magill "elephant trunk" (figure 1) and, for children, the Ayre T tube (figure 2).[2]

In cases involving thoracic injuries, which may also, of course, interfere with respiration, endotracheal intubation is desirable but not essential. It may be necessary to assist the natural respiration or to administer artificial respiration even before the anesthetic is given. Gentle inflation of the lungs by means of a bag and mask and oxygen may keep the patient alive until preparations for the operation are made.

*Fullness of the stomach*—It may usually be assumed that an accident victim has a full stomach, since gastric emptying stops at the time of the accident. I have seen enormous amounts of partially digested food come from stomachs that had had no intake for more than 24 hours. Aspiration of the gastric contents by the patient may cause fatal laryngospasm, tracheitis, pneumonia or lung abscess. The stomach can be evacuated in any of several ways. Emptying the stomach by means of an ordinary gastric tube or even a large-bore Ewald tube is not sufficient. A garden hose *might* work if you could get your patient to hold still for it. Forced vomiting by stimulating the gag reflex may be helpful. The safest procedure, we have found, is to anesthetize the nose, pharynx, glottis and trachea with a topical anesthetic while the patient is awake. Insert a cuffed endotracheal tube and inflate the cuff before administering the general anesthetic. Most patients tolerate this procedure very well, especially if they understand that it is necessary for their safety. Insertion of a large cuffed tube into the esophagus with inflation of its cuff before the patient is anesthetized is another recommended procedure.[3]

If the patient is uncooperative, it may be necessary to anesthetize him before the tube is inserted, a procedure that involves a calculated risk. The patient should be placed on a table that can be tilted so that his head is down, and he should preferably be anesthetized in the lateral or even the prone position. A metal suction tip rather than a catheter should be used to provide suction. After the patient has been adequately anesthetized, the endotracheal tube should be put into place and the cuff inflated. "Silent" or imperceptible regurgitation is likely to occur during anesthesia, regardless of the anesthetic agent or the site of operation.[4] If feasible, regional anesthesia—spinal, field block or nerve block—would eliminate this danger.

### *Preanesthetic Medication*

In the injured patient preanesthetic medication should be kept to a minimum. Barbiturates



UNIVERSITY OF MICHIGAN LIBRARIES

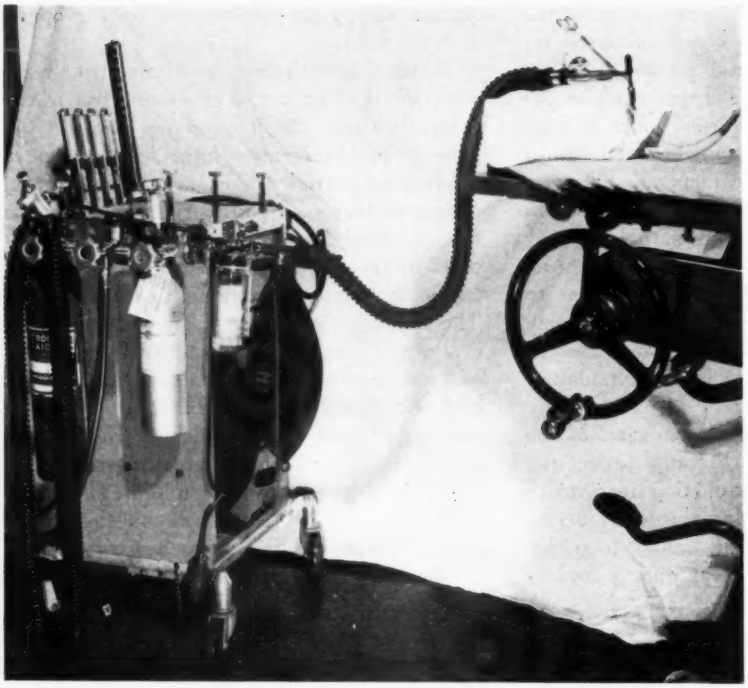


FIGURE 1. Magill attachment with nonrebreathing valve attached to an endotracheal tube.

FIGURE 2. Ayre's T tube attached to the endotracheal tube for a child.

may precipitate shock, and opiates should be avoided[5] except when the patient is in extreme pain, since they too may precipitate shock or interfere with inhalation anesthesia by depressing respiration. Before inhalation anesthesia is administered a belladonna derivative should always be given; atropine is preferred because it produces fewest side effects. Scopolamine, in the presence of pain, may cause disorientation and an uncooperative patient. We avoid scopolamine in small children and in elderly patients because of the disorientation which may occur postoperatively.

### *Selection of Anesthetic Agent*

The first consideration in choosing an anesthetic agent is the patient's safety, which may or may not coincide with such other factors as the patient's comfort or the convenience or preference of the surgeon or anesthetist.

*Shock*—For the patient who is or has been in shock or potential shock, the anesthetic agent must not depress blood pressure or

cardiac action. This immediately rules out agents administered intravenously. Chloroform and two of the newer inhalation agents, FLUOROMAR® and FLUOTHANE,® profoundly depress the circulation; diethyl ether depresses blood pressure levels in the deeper planes of anesthesia, particularly in patients with decreased blood volume.

For patients in shock, our choice of anesthetic, based on our familiarity with its mode of action, is usually cyclopropane. As the only anesthetic agent that does not cause dilatation of the arterioles,[6] it supports blood pressure except in very deep planes of anesthesia. It also acts rapidly and permits pleasant induction and prompt recovery. Adequate relaxation of the patient generally occurs with cyclopropane, but a specific relaxant may be used when necessary. Succinylcholine is preferred because, of all the curariform compounds, it has the least effect on blood pressure. Nitrous oxide is the most innocuous of all the inhalation agents, *if oxygenation is not impaired.* Provided the anesthesiologist is familiar with the procedure, another good technic for the patient in shock is the administration of nitrous oxide combined with succinylcholine.

*Cardiac disorders*—The condition of the patient's heart should be determined, if possible, before the anesthetic is administered. The patient with severe mitral stenosis represents a poor risk for anesthesia. First, he cannot tolerate belladonna except in minimal doses, since the vagal-blocking action of the belladonna drying agents may speed the pulse rate, resulting in shortened diastole and poorer filling of the left ventricle. Second, the patient with mitral stenosis is extremely susceptible to anesthetic agents and depressant drugs, and therefore only minimal amounts of these agents are needed. Furthermore, barbiturates and curariform compounds are contraindicated because they further decrease the pulse pressure.

The patient with a history of myocardial infarction should be observed carefully during anesthesia. Lowered levels of blood pressure, particularly of the diastolic pressure, could be fatal. Adequate oxygenation is necessary. Here again we customarily choose cyclopropane, since oxygen is given with it in high percentage, and peripheral pooling of blood does not occur. Serious cardiac arrhythmias do not develop with cyclopropane anesthesia, provided ventilation is adequately assisted and carbon dioxide carefully removed.[7,8] Vasopressors should not be used during cyclopropane anesthesia,[9,10] and evidence suggests that they also should not be used in the treatment of shock.[11] In fact, vasopressors may induce irreversible shock in animals with decreased blood volumes due to hemorrhage. Repeated small doses of vasopressors may also cause irreversible shock in animals with normal blood volumes.[12] Digitalis should be administered rapidly to the patient with cardiac decompensation either before or during induction of anesthesia.

*Injuries to the spinal cord and head*—Injuries to the spinal cord and peripheral nerves do not markedly affect the choice of anesthetic. Injuries to the head may influence the type of anesthetic administered since respiration may be affected. Opiates are contraindicated when intracranial pressure is increased. Since intracranial injuries make it impossible for the neurosurgeon to clamp and tie bleeding vessels, he must rely heavily on the use of the electrocautery, which immediately demands that the anesthetic be nonexplosive. In our neurosurgery operating room, the "workhorse" is nitrous oxide, alone or in combination with many other agents. A basal anesthetic with tribromoethanol or thiobarbiturate may be given rectally. Other commonly used nonexplosive supplements to nitrous oxide are chloroform, Fluothane and trichloroethylene. Small intermittent increments of thiobarbiturate and, occasionally, of opiates are administered intravenously.

### *Method of Administration*

Before choosing intravenous agents one should ponder the results of a recent survey of anesthetic agents given to more than one-half million patients in 10 university hospitals.[13] Causes of death were assigned to the disease, the surgical procedure or the anesthetic. Anesthesia was the principal cause of death in 1 of every 2,680 instances and a

UNIVERSITY OF MICHIGAN LIBRARIES

contributing cause in 1 of 1,560 other cases. The death rate among patients who received relaxants intravenously was six times as great as among those receiving inhalation agents; 37 per cent of the deaths from intravenously administered relaxants occurred in spite of adequate artificial respiration. Among patients receiving thiobarbiturates intravenously, the mortality was four times as great as among those who did not.

It should be noted that trichloroethylene cannot be used with an absorption system because it reacts with soda lime to form dichloracetylene. The use of cyclopropane in a system that has a one-way exhalation valve is too expensive.

When choosing the method of administration, some considerations recur, including the safety of the patient, the fullness of the stomach, and the site of injury. In addition, the agent chosen must be considered.

Whenever possible, we have found it desirable to use some sort of absorption chamber. This gives some assurance—although not a 100 per cent guarantee—that carbon dioxide will be removed from the anesthetic atmosphere. But there are many inefficient types of canisters, the soda lime must be kept fresh, and many valves on circle absorbers prove faulty when accurately tested. If absorbers are not used, a flow of gases amounting to at least 10 l. per minute is necessary to blow off the carbon dioxide. A nonrebreathing valve, such as the Stephen-Slater[14] or Fink[15] valve, will eliminate all expired air, if ventilation is adequate. Whatever method of eliminating carbon dioxide is used, alveolar ventilation must be satisfactory or acidosis will develop.

### *Summary*

Anesthesia for accident victims is extremely hazardous since the patient is ill prepared, sketchily evaluated, and will usually present problems not present in "everyday anesthesia." Therefore the patient's condition before the accident and the condition resulting from the accident should be carefully evaluated.

The patient's circulatory status is probably the most important consideration. Proper precautions should be taken to prevent circulatory failure and to treat it should it occur.

Adequate respiration should be maintained throughout and should be assisted whenever it becomes depressed.

### REFERENCES

1. Gillespie, N. A.: Endotracheal Anaesthesia. Madison, Wisconsin, The University of Wisconsin Press, 1948, pp. 146-149.
2. Ayre, P.: Endotracheal anesthesia for babies. Anesth. & Analg. 16:330 (November-December) 1937.
3. Giuffrida, J. G. and Bizzari, D.: Intubation of the esophagus. Am. J. Surg. 93:329 (February) 1957.
4. Berson, W. and Adriani, J.: "Silent" regurgitation and aspiration during anesthesia. Anesthesiology 15:644 (November) 1954.
5. Eckenhoff, J. E. and Helrich, M.: Study of narcotics and sedatives for use in preanesthetic medication. J.A.M.A. 167:415 (May 24) 1958.
6. Hershey, S. G., Zweifach, B. W. and Rovenstine, E. A.: Effects of depth of anesthesia on behavior of peripheral vascular bed. Anesthesiology 14:245 (May) 1953.
7. Lurie, A. A., Jones, R. E., Linde, H. W., Price, M. L., Dripps, R. D. and Price, H. L.: Cyclopropane anesthesia. Anesthesiology 19:457 (July) 1958.
8. Johnstone, M.: Cyclopropane anaesthesia and ventricular arrhythmias. Brit. Heart J. 12:239 (July) 1950.
9. Orth, O. S., Stutzman, J. W. and Meek, W. J.: Cardiac action of sympathomimetic amines in cyclopropane, ether and chloroform anesthesia. Am. J. Physiol. 126:595 (July) 1939.
10. Orth, O. S., Leigh, M. D., Mellish, C. H. and Stutzman, J. W.: Action of sympathomimetic amines in cyclopropane, ether, and chloroform anesthesia. J. Pharmacol. & Exper. Therap. 67:1 (September) 1939.
11. Frank, E. D., Frank, H. A., Jacob, S., Weizel, H. A. E., Korman, H. and Fine, J.: Effect of norepinephrine on circulation of the dog in hemorrhagic shock. Am. J. Physiol. 186:74 (July) 1956.
12. Freeman, N. E., Freedman, H. and Miller, C. C.: The production of shock by the prolonged continuous injection of Adrenalin in unanesthetized dogs. Am. J. Physiol. 131:545 (January) 1941.
13. Beecher, H. K. and Todd, D. P.: A Study of Deaths Associated With Anesthesia and Surgery. Springfield, Illinois, Charles C Thomas, 1954.
14. Stephen, C. R. and Slater, H. M.: A nonresisting nonrebreathing valve. Anesthesiology 9:550 (September) 1948.
15. Fink, B. R.: A nonrebreathing valve of new design. Anesthesiology 15:471 (September) 1954.

# Crisis Types of Abdominal Pain

WALTER C. ALVAREZ

*Chicago*

*When constant and widespread abdominal pain is not influenced by eating, defecating or passing gas, it is probably of central origin. An observer should recognize that there is little likelihood of an abdominal lesion in frequent episodes of severe abdominal pain which terminate spontaneously and in which the abdominal wall is soft. A hysterical element is sometimes observed in this syndrome. A carefully elicited history is helpful in diagnosis.*

WALTER C. ALVAREZ

EVERY so often in my medical youth, I was much puzzled on seeing a patient in an attack of severe abdominal pain plus retching. Sometimes I became so uneasy that I advised an exploratory operation, which showed nothing. Gradually, through the years, I saw enough cases to learn, first, to recognize the clinical picture of a "gastric crisis," and, then, to take the sort of history that could show me I was dealing not with an abdominal disease but with a "storm" coming out of the brain.

Then I came to see that these people often are much depressed and apathetic from the *start of a spell*. They look like a person with a severe sick headache. Usually the abdominal wall is remarkably soft and relaxed; as in migraine, the retching brings up very little; there is no fever; the pulse may be almost normal; the leukocyte count is low; a scout film shows nothing wrong, and usually morphine does not help much, which suggests a pain of central origin. In a few cases, the wide and vague distribution of the abdominal pain shows that it is arising in the brain. It may begin in the pelvis and run up both sides of the abdomen, along the outer sides of both breasts into the axillae, and also down the outer sides of the thighs.

Usually the history alone is enough to tell the physician that he need not have the abdomen explored. In most cases, he will learn that in the past, starting perhaps in childhood, the patient has had any number of similar spells. They usually last from 12 to 48 hours, and then clear up, leaving no residue. Obviously, then, they are episodic, like attacks of migraine. Usually by the time a consultant sees

the patient, most often a woman, she has had her abdomen explored once or twice with negative results. The fact that I keep seeing such patients who have had from 3 to 10 exploratory operations makes me feel there is still need for writing a paper on the subject.

Refuting the idea that there is a lesion in the wall of the digestive tube are the facts that these persons have perfect digestion between episodes and that their pain is never influenced by eating, emptying the colon or passing gas. Sometimes in diagnosing a functional trouble, it helps to learn that the spells tend to follow some annoyance, strain or fatigue, such as commonly triggers a sick headache.

### *Possible Causes of a Gastric Crisis Type of Pain*

*Neurosyphilis*—Naturally, in all cases here described, neurosyphilis was ruled out.

*Migraine*—On abstracting the records of several hundred cases of severe migraine, I was surprised to find how large a percentage of the patients had had repeated spells of abdominal pain for which no local cause was ever found, even at an exploratory operation. The diagnosis of migrainous pain is usually easy if one will only ask and get the (usual) history of sick headaches in the person's youth. In middle life these spells often fade out, perhaps to be replaced by the spells of abdominal pain. None of these patients would ever have undergone an exploratory operation if the physician had only asked one question: "Just before your abdominal pain starts, do you get a pain in or around one eye, perhaps followed by a unilateral headache?" If the answer is "Yes" and if the patient's family has a high tendency to migraine, the abdominal crises are almost certainly migrainous in origin. Sometimes, then, one can block them with an injection of GYNERGEN®, and that will clinch the diagnosis.

*Migraine plus something else*—In many cases of severe migraine with abdominal crises, I find the patient has a migrainous inheritance from one parent and an epileptic, psychotic or alcoholic inheritance from the other parent.

*Epilepsy*—Often one must consider whether the abdominal crises are due to epilepsy. It helps greatly to learn, by very tactful questioning, that the patient has one or more relatives who have had "fainting spells," or who have a violent temper, or some form of psychosis; or to learn that the patient has a violent temper or had convulsions in childhood or has always had terrible nightmares, nameless fears, fears of attacking someone, or occasional brief "blackouts." Electroencephalograms should be made in such cases, and if they show spikes or signs of seizure activity, the diagnosis is certain. Sometimes an anticonvulsive drug such as DILANTIN® sodium will help these patients.

*Psychosis*—Until I reviewed and abstracted the records of 574 nervous patients who had psychotic or alcoholic relatives (1958), I had no idea how often mildly psychotic persons with a bad nervous ancestry have bouts of severe abdominal pain. As all psychiatrists know, apparently sensible persons who are going insane often complain mainly of abdominal pain. I have seen depressed persons lose their supposed subacute appendicitis in a week after three or four electroshock treatments had driven away their melancholia.

*Hysteria*—There are cases in which hysteria plays a part in producing the spells. A woman may go into a semicomatose state or thrash about or clown a bit. She may become markedly bloated and have abdominal pain without excessive gas in her bowel.

*Emotional storms*—Occasionally one will see a highly emotional person who will go into a gastric crisis after a tantrum of temper.

*Food allergy*—I have seen an occasional rare case in which recurrent attacks of severe abdominal pain were due to a food or a drug allergy, but usually the clinical picture was not that of a gastric crisis. With the drug phenolphthalein, I once saw a chill, fever and a skin eruption, and with food allergy due to blue cheese in salads, I saw a good deal of shock.

*Little strokes*—I have seen many elderly patients with a little stroke who had such severe rending abdominal pain that an exploratory operation was advised. In these cases, the physician seldom need fear the presence of an abdominal lesion, because, when elicited, the

story of a slight stroke is so typical and so easily recognizable.

*Porphyria*—In a rare case, one will see a person who has spells of such severe abdominal pain that an operation is considered. Because an operation under PENTOTHAL® sodium anesthesia can produce a potentially fatal flare-up of the disease, one should keep porphyria in mind. The diagnosis should be suspected when, besides the abdominal pain, the patient has several neurotic and even mildly psychotic symptoms, with perhaps several paresthesias and, rarely, a great hypersensitiveness of the skin to sunlight. The symptoms are likely to flare up if the patient takes a barbiturate, and the urine may then turn red if exposed to sunlight. In doubtful cases, the titer of porphyrin in the urine should be measured.

*Peritonism*—This is a rare, hereditary, episodic disease seen in Jews, Armenians, Syrians and Egyptians. At intervals the patient has what looks like a painful peritonitis or perhaps pleurisy which lasts for two or three days. The clinical picture is sufficiently different from that of a gastric crisis to eliminate confusion.

*Posterior perforating duodenal ulcer*—The severe pain of a posterior perforating duodenal ulcer is usually associated with a soft abdominal wall, due to the fact that the abscesslike mass is behind the peritoneal sac. The clinical story is usually that of pain every night for months. The disease is not episodic, with intervals of perfect health, and the patient is usually emaciated.

*Cases of undetermined cause*—Occasionally one will see a patient with typical recurrent gastric crises, the cause of which cannot be determined.

### *Case Reports*

*Possible migrainous equivalent*—A 40 year old married woman who was typically migrainous complained of having had many spells of "terrible" abdominal pain, with violent retching, fainting and "much gas." She would be cold and clammy all one day, and during this time would act like a hysterical person in a semicoma, failing to answer questions. The spells I saw resembled gastric crises. I was sure the storm was arising in the woman's brain; the only question was, why was she affected physically?

Sometimes she had a milder type of spell limited to a widespread "misery" in her epigastrium, bloating and repeated belching. During some spells she would be extremely irritable and quarrelsome. Often she would wake in pain at 6 A.M. and would rush to the bathroom for three or four bowel movements. She could not think of any psychic cause for her trouble. She said she had a good husband, a good home and nothing to bother her. My impression was that the basic cause was her migrainous temperament.

*Severe migraine plus a mild psychosis*—Case 1—An odd and eccentric, but likable 45 year old married woman was seen on several occasions when she went into what I thought was a gastric crisis. She said her spells often were so severe that on two occasions surgical exploration had been done with negative results. What impressed me was that, at the beginning of each spell, the woman would go into a semicomatose state in which, for two or three days, she would lie on her bed, uncommunicative, apathetic and almost unconscious of her surroundings. During this time, if one kept asking her questions, she would mumble and talk very slowly like a person heavily drugged. She might even be somewhat aphasic. Evidently her brain was much affected at the beginning of each spell.

Eventually I learned that in her early life she had been highly migrainous. Furthermore, her gastric crisis would always start with a typically migrainous pain back of one eye, and great annoyance with a mean psychotic husband triggered the storms. In addition to her migrainous inheritance, she had a bad psychotic one from insane forebears. As a result, she had always been somewhat odd and had a bizarre and very severe type of migraine. Years later she told me that her spells had ceased the day she divorced her trouble-making husband.

Case 2—A neurotic, but pleasant and sensible business woman had lost much weight and had become a chronic invalid because of frequent gastric crises requiring morphine for

relief. Even after 10 days of questioning, I could not guess what her basic trouble was; for, in addition to her abdominal pain, she had weird, schizophreniclike "distresses" all over her body. Finally, light broke when she admitted that before a gastric crisis she would always get a severe pain in one eye. Knowing this, the next time she started to go into a spell, I gave her an injection of Gynergen, and this blocked the storm.

Later I learned that the reason she had become so badly debilitated in the course of two years was that she hadn't had time to recover from one severe spell and regain her weight before she was in another. When the spells were blocked with Gynergen, she rapidly regained her former weight and strength, and she soon was back in her store running her business. Then she told me that sudden panics of fear that she was going insane like her mother had triggered the frequent spells.

*A carrier of epilepsy*—Case 1—An able attorney complained of many spells of a gastric crisis type of abdominal pain. Every test that could be given him in several big clinics had failed to show anything wrong.

Because at times the man had a constant headache (which, in my experience, is often of psychic origin); because at times he became mentally dull and so irascible he was ashamed of his outbursts, and because a hard game of handball every day would do much to keep him from going into his spells, I suspected epilepsy. I kept asking him about his forebears until one day he broke down and told me about them. His mother's sister was a cruel, sadistic person, a "devil," who eventually committed suicide. The mother's father was a violent, hot-tempered man, who looked like a degenerated epileptic. Several of the patient's brothers were alcoholics; several were violent persons, and one had epilepsy with seizures. The patient had never experienced a "blackout."

As I expected, when electroencephalograms were made, they were typical of epilepsy. The only sad feature was that Dilantin sodium did not cure him.

Case 2—One of the most irascible and violent persons I ever knew was a Latin American physician who said he had a hard time keeping any practice, because he hated everyone and it was hard for him to keep from attacking people. For years, he had been having gastric crises.

Although his electroencephalogram was typical of epilepsy, he had never had a seizure. There were several alcoholics in his father's family. The father had a brother who was epileptic, alcoholic and mentally retarded, and a sister who was born deaf. The father's three other brothers were all violent men—one so homicidal he lived as a recluse to avoid killing someone.

*Epilepsy*—A 40 year old unmarried woman complained of spells of "terrible" epigastric pain with retching which proved to be of the gastric crisis type. Certain facts suggested the cause was in her brain; for example, a dose of morphine could throw her into a crisis; she soon came out of a spell without any treatment; in a spell her abdominal wall was soft, and removal of her stoneless gallbladder had done no good.

After much questioning, I learned of several psychotic and morphine-taking relatives from whom she probably inherited her unstable nervous system. Later I learned what she had vowed never to tell, namely, that she had had several attacks of grand mal. As I expected, Dilantin sodium greatly improved her health.

*Fear of going insane*—A 29 year old man, who usually weighed over 200 lb., complained of a gastric crisis type of pain and vomiting. In his spells he would quickly lose from 60 to 70 lb. in weight, which would be rapidly regained. At times he was in such pain he was given morphine.

When I was first asked to see him, he was in such distress that a surgeon was about to explore his abdomen. However, the doctor sensed something was neurologically wrong, and he asked for a consultation. With great difficulty and only after long interviews did I learn that the man had had severe attacks of migraine in his youth. Then, one after the other, he had three attacks of severe depressions, alternating with spells of mania. In each of his depressive attacks, the severe abdomi-

nal pain had come with his terrifying fear of going insane. He feared insanity because a number of his relatives were in mental hospitals. Because with his fear the man stopped eating, he rapidly lost weight.

This case shows how impossible it often is to make any sort of diagnosis until, after several interviews, the patient tells the really important story. This man told me that he had seen many physicians, but had always concealed his psychosis because he was so ashamed of it. I would never have obtained the story, if I hadn't sensed from past experience that there was one and if I hadn't kept questioning the man day after day until I got the truth.

*Psychotic depression*—Case 1—For 25 years, an odd and eccentric woman had been going from physician to physician complaining of severe abdominal pain of a crisis type. She often needed morphine. The tendency of this pain to wander widely from her left scapula to her left groin had satisfied me that the cause must be psychic. Able men had examined her and had found no local cause. I learned that the storms came whenever she was very tired. Later, after we had become friends, she admitted that she was mentally unstable and, at times, psychotic. A year later, her people wrote me that she had had to be committed. I have seen several such persons slowly going insane who, for many years, complained principally of a gastric crisis type of pain.

Case 2—A 40 year old woman had crises of abdominal pain which I was able to study for some six months. I knew she was depressed, because in the office she sometimes broke down and cried. But she maintained that anyone who had had pain as much as she had had and who was fearing death and the leaving of her children to the mercies of strangers should be depressed. I am ashamed to say that it took me several months to see that her depression was primary and her pain secondary. Then I referred her to a psychiatrist who gave her a few electroshock treatments, which not only banished her depression, but instantly put an end to her crises of pain.

*Poor nervous inheritance and much psychic strain*—A puzzling case was that of an unmarried and asexual South American woman, aged 37. She came of a distinguished family, but she had several insane relatives and a sister who was a mongoloid. There was no migraine in the family.

Three years before I saw her, the woman began to have severe gastric crises. Her mother could tell two or three days before that a spell was coming, because the daughter looked anxious. At first this woman would get a feeling of great unrest and fear; then would come epigastric pain and dyspnea which would spread up through her thorax to her neck. She would then have to sit up in bed. She would feel as if her chest would explode, and she would get a binding sensation in her abdomen. At times she needed morphine, and she would walk the floor all night. There was never any nausea or vomiting, fever, chill, bloating or headache. The abdominal wall would remain remarkably soft. A spell would come every 20 or 25 days and would last from six to nine hours.

Eventually I learned that 12 years before, on becoming a nun, she had run into distressing conflicts of opinion with her very dictatorial Mother Superior. After years of unhappiness, she had left the order; and following this, she had begun to have the attacks of pain.

With rest and reassurance the spells ceased, and a year later she wrote that she had remained well. It would appear, then, that the spells were of the type I see frequently in neurotic relatives of the insane.

Case 2—Another young Colombian woman, a secretary in her early thirties, was seen by me in several gastric crises. In this case, also, there was insanity in the family and much unhappiness in the patient's life. Because severe coxitis in both hips kept her in the hospital for several months, I had a good chance to study her until I was satisfied the pain was arising in her brain and not in her abdomen. Her spells had started when her home physician troubled her terribly by diagnosing hereditary syphilis. Actually she had no sign of this disease, and four of the best tests for syphilis gave negative results. Fortunately, after a few months, the spells ceased.

*A rare type of hysteria*—I will never forget two unusual women who for years were unable

to do anything or go anywhere because of frequently recurring severe crises of abdominal pain, usually without retching. Their spells were atypical and almost unique. In the case of one woman, at the start of a spell the abdominal wall would suddenly become boardlike and would stay that way for several hours. During this time, the woman would have severe intermittent laborlike pains. Finally, there would be a loud gurgle, and with this, the attack would end. The abdominal wall would suddenly again be soft. The pains were so severe that the woman soon became addicted to morphine. After the patient had been an invalid for many years, her mother died. She then recovered and went to work. I had reason to believe she hated her mother and was punishing her.

The other patient had also been a chronic invalid for years. In a crisis of pain, there would be a hysterical type of abdominal bloating, and the muscular wall would become tense. She also had laborlike pains. She recovered completely the day her alcoholic husband died. She may have been using her illness to fend him off.

*An easily upset, overly sympathetic woman*—A 35 year old, overweight, married woman had repeated spells of severe abdominal pain with vomiting. These spells lasted a day, and morphine did not help much. The abdominal wall was typically soft. Eventually I learned that she was an extremely intense and emotional sort of person who often went to pieces nervously, usually in sympathy with the troubles of some relative or close friend. To show me how sympathetic she was, she said that when her brother lost his money, she cried for three weeks! By controlling herself better, she avoided the spells.

*Emotional storm*—I have seen a number of cases in which the patient had an occasional gastric crisis following an emotional storm. Typical was the case of an artistically inclined man who, on the death of his father, was condemned to run the large family store. Every so often he would come home in the late afternoon in great abdominal pain. He would start retching, and about 3 A.M. he would be rushed to a hospital to be operated on for a supposed intestinal obstruction. Nothing was found in four such exploratory operations. From his wife I learned that all his spells had followed his "blowing his top" at an erring employee. When on vacation or when mentally at peace, he had perfect health.

A hot-tempered and migrainous nurse was brought to me by the surgeon for whom she worked. On two occasions he had operated for intestinal obstruction and had found nothing. When I saw her alone, the woman confessed that the first spell came when the handsome scamp who had promised to marry her hadn't shown up at the church. The second spell came when, after promising to marry another man —on the "rebound"—she had begun to cry violently and had had to call off the wedding.

*Crises of unknown cause*—Case 1—A stocky, pleasant, successful and apparently well-adjusted business man, aged 57, reported that for 23 years he had had severe spells of abdominal pain. I saw him in two of his attacks and was satisfied they were of nervous origin. His home surgeon had explored his abdomen and had found nothing.

The spells had started when the patient was 34 years old. The first attack, like all subsequent ones, came without warning. They came at any time of day or night, with no aura, and most often when he was tired from overwork.

First would come salivation, then griping and rhythmic laborlike pains just below his navel, and 30 minutes later, retching, which would recur at 15 minute intervals. Morphine did not help much. During a spell he would lose 10 or 15 lb. In the attacks I saw, the abdominal wall was so soft I could easily palpate the front of the man's spine. There was no increase in his temperature, pulse rate, white cell count or red cell sedimentation rate.

Between spells he had perfect digestion. There was nothing in his story to suggest migraine, except that two brothers and a niece had sick headaches. My patient's spells were not influenced by ergotamine. They were sometimes aborted by the use of a suppository of NEMBUTAL®, inserted the minute an attack started. There was nothing to suggest epilepsy. Unfortunately I was unable to have an electroencephalogram made. Later the man wrote to

say that by taking ½ gr. phenobarbital daily he could go for long periods without a spell.

Case 2—A nice, sensible, untroubled woman appeared to have colic caused by a gallstone with pain so severe as to require morphine for relief. However, the gallbladder functioned well, and two surgical explorations showed nothing wrong. The pain then became crisis-like and episodic, and for the next 20 years I kept seeing her at intervals because of her great abdominal distress. That there was a widespread nervous storm was shown by the fact that, with the pain in her abdomen, there was often numbness in two fingers of her right hand, and sometimes Raynaud's syndrome was present. After some years, the pain changed and became a widespread "misery," which remained constant day and night for years. Typical of a functional "distress" was her feeling that she would like "to reach in and turn something over." Because of the long duration of her illness, I was sure that the disease was nervous in origin, but I could never guess what the basic cause was.

### *Summary*

Through the years a busy consultant sees a number of remarkable cases in which the patient has spells of severe abdominal pain with violent retching. The spells, which resemble gastric crises, will come perhaps every few weeks and will terminate spontaneously, usually in from one to three days. In a spell the abdominal wall is remarkably soft. There is no suggestion of peritonitis or of any lesion in the abdomen. In most cases surgeons have explored the abdomen and have found nothing.

A good observer will soon learn to quickly recognize the syndrome. The diagnosis is largely made when one learns that the spells have been recurring at intervals, perhaps for years. The cause must be in the nervous system. Usually morphine does not help much. Sometimes the pain spreads up along the chest or down along the outsides of the thighs.

Often as a spell starts, there is much apathy, like that of a woman in a bad attack of migraine. Sometimes one can recognize a hysterical element in the syndrome.

It can help greatly to know that the patient used to be highly migrainous; that the spells follow the sort of stimuli that trigger sick headaches; and that they begin with a pain back of one eye. Often the physician will learn that the patient inherited migraine from one parent and a mild psychosis from the other parent. When there is epilepsy in the ancestry, an electroencephalogram must always be made. When it shows dysrhythmia with seizure activity, Dilantin sodium will sometimes effect a cure. Some mildly psychotic persons or persons going insane complain much of abdominal pain.

In some cases the physician must think of hysteria, hysterical nongaseous bloating, food allergy, porphyria, peritonism or a little stroke.

Abdominal pain which sometimes becomes a constant and widespread "misery" is probably always of central origin. When an abdominal pain is not influenced by eating or defecating or passing gas, there is little likelihood of a lesion in the digestive tract.

Some crises of abdominal pain come when a mildly psychotic patient goes into a panic, fearing he is going insane as did his mother or some other relative.

### REFERENCES

ALVAREZ, W. C.: Abdominal pain due to intracranial disease. Am. J. Digest. Dis. 3:349-350, 1936.

_____: What causes flatulence? J.A.M.A. 120:21-24, 1942.

_____: A rare syndrome of crisis-like abdominal pain. Gastroenterology 4:296-304, 1945.

_____: Hysterical type of non-gaseous abdominal bloating. Arch. Int. Med. 84:217-245, 1949.

_____: Violent reaction to phenolphthalein. California Med. 71:38, 1949.

_____: Practical Leads to Puzzling Diagnoses; Neuroses That Run Through Families. Philadelphia, J. B. Lippincott Company, 1958.

# Clinical Re-evaluation of Daytime Sedatives

ROBERT C. BATTERMAN, ARTHUR J. GROSSMAN, PAUL LEIFER* AND GEORGE J. MOURATOFF†

*New York Medical College-Metropolitan Medical Center, New York*

*Phenobarbital, butabarbital sodium, acetylcarbromal, glutethimide, meprobamate and prochlorperazine were evaluated under conditions of clinical practice to determine their relative effectiveness in producing daytime sedation, nighttime hypnosis by multiple daytime dosages, and combined daytime sedation and nighttime hypnosis. A therapeutic index (per cent effectiveness: per cent untoward reactions) was established for each drug. Butabarbital sodium provided the highest rating of sedatives studied for control of anxiety and insomnia by daytime dosages.*

ROBERT C. BATTERMAN

THE multiplicity of functions of the central nervous system and the various areas or centers involved emphasize the need for reclassifying the sedative drugs. In the broadest sense sedative drugs are defined as agents which depress the central nervous system. This depression may be general or may involve a specific brain center. However, a drug which depresses a specific function of the central nervous system may not be a true sedative. For example, although analgesics may depress lower subcortical areas by sensory blockade as part of their pharmacologic action, and although there may be an overlapping of pharmacologic action and hypnosis, analgesic agents per se would not be classified as sedatives. Similarly, other depressant nonsedative drugs include the antitussives, antiemetics, anticonvulsants, and psychotherapeutic or ataractic medications. Although the latter possess different sites or mechanisms of action, they are best considered to be normalizers of mental and behavioral activity.

True sedatives produce a gradient of response dependent on potency, dose and locus of action. The most potent can provide any lesser degree of sedation by means of progressively lower doses. A less potent sedative cannot achieve maximal sedation, short of toxicity, regardless of dose. The maximal degree

*Department of Medicine, New York Medical College-Metropolitan Medical Center, New York, New York.

†Fellow in Medicine, Department of Hospitals, New York, New York.

of depression, with loss of consciousness and depression of all cortical centers, is anesthesia. The next degree, that of hypnosis or soporific effect, represents sleep without alteration of motor activity and sensory perception. A still lesser degree is drowsiness without sleep.

The confusion that exists in regard to sedative agents revolves about the terms tranquilizer and daytime sedative. We contend that these medications differ from psychotherapeutic agents. Daytime sedation quiets or counteracts an overstimulated central nervous system and restores normalcy without daytime drowsiness, analgesia, or alleviation of mood or behavior, except as a normal sequela to physical and mental relaxation. Sedatives are indicated whenever symptoms of anxiety or tension result from emotional, physical or situational stress rather than from intrinsically abnormal mental processes. To be satisfactory as tranquilizers or sedatives for daytime control of the anxiety state, medications should meet the following requirements regardless of overlapping pharmacologic actions:

1. There should be high predictability that the usual therapeutic dose will produce satisfactory control of a specific anxiety state or a distressing symptom complex within a reasonable period of time.

2. Sedation must neither be preceded or replaced by cerebral stimulation nor followed by a "hang-over" or other manifestations of prolonged effect.

3. Control of distressing symptoms should be produced without daytime drowsiness, impairment of mental processes, sluggish movements or loss of libido.

4. The therapeutic dosage should not influence the cardiovascular and respiratory systems or the liver or renal function, or depress any vital function of the body.

5. Chronic administration, as required in the majority of patients, should not result in cumulative toxicity affecting the central nervous system (excitement, toxic psychosis, neurologic dysfunctions), the blood-forming organs (agranulocytosis, megaloblastic anemia, thrombopenic purpura, aplastic anemia), the liver (jaundice), or the kidney (antidiuresis, nitrogen retention).

6. Precautions in administering the drug should not be required because of an underlying disease state, the patient's age, or the functional capacity of the liver or kidneys, which might play a role in the excretion, metabolism or dissipation of the drug.

7. The medication should be easily administered and well tolerated.

8. Idiosyncrasies should be either nonexistent or rare.

9. The medication should ensure continuous control of distressing symptoms without development of tolerance.

10. The risk of habituation or addiction, or both, should be minimal or nonexistent.

The purpose of this investigation was to determine which representative agents currently used for controlling anxiety states most nearly meet the specifications outlined for an ideal sedative.

### *Method and Selection of Patients*

One hundred and sixty-eight ambulatory outpatients with clearly defined symptoms of anxiety and nervous tension were observed and treated over a five year period. The symptoms usually encountered and which we required to be present in various combinations and degrees were "jitteriness," nervousness, irritability, headache, weakness, palpitations, restlessness, fatigue, listlessness, apprehension, "stomach distress," an excitable "on-the-go" feeling, an inability to relax, breathlessness, excessive sweating, buzzing in the ears, visual blurring, dizziness and "tightness" in the body. There was usually associated insomnia, reflected by difficulty in falling asleep, interrupted sleep, or an insufficient period of sleep. None of the patients had an organic sleep disturbance with reversal of the sleep pattern. The majority of patients had an underlying musculoskeletal condition, but during the time of sedative evaluation the pain and disability of the arthritic condition were minimal and did not require analgesic or antirheumatic drugs which might have interfered with the medications under study. Since an evaluation of this type involves duplicating the conditions under which such therapy is actually used in everyday practice, there was no selection of patients

TABLE 1

COMPARATIVE EFFECTIVENESS OF DAYTIME SEDATIVES

| MEDICATION | DOSE (*Three or four times daily*) | NUMBER OF PATIENTS | SATISFACTORY DAYTIME SEDATION | | UNTOWARD REACTIONS (*Per cent*) | THERAPEUTIC INDEX* |
|---|---|---|---|---|---|---|
| | | | *Number of patients* | *Per cent* | | |
| Placebo | 1 tablet | 44 | 14 | 31.8 | 12.4 | 2.5 |
| Phenobarbital | 15 mg. | 30 | 18 | 60.0 | 30.0 | 2.0 |
| | 30 mg. | 20 | 14 | 70.0 | 35.0 | 2.0 |
| Acetylcarbromal | 200 mg. | 28 | 15 | 53.5 | 21.4 | 2.5 |
| Butabarbital sodium | 15 mg. | 40 | 26 | 65.0 | 10.0 | 6.5 |
| | 30 mg. | 53 | 29 | 54.7 | 16.4 | 3.3 |
| Glutethimide | 125 mg. | 32 | 21 | 65.6 | 15.6 | 4.2 |
| | 250 mg. | 31 | 11 | 35.5 | 50.0 | 0.7 |
| Meprobamate | 400 mg. | 33 | 12 | 36.3 | 26.5 | 1.3 |
| Prochlorperazine | 5 mg. | 34 | 13 | 38.2 | 20.0 | 1.9 |

*Per cent effectiveness: per cent untoward reactions.

other than to eliminate those with an abnormal mental or behavioral problem.

Six widely used sedatives or tranquilizers and a placebo were studied in 357 trials. The drugs used consisted of 15 and 30 mg. doses of phenobarbital, 15 and 30 mg. doses of butabarbital sodium, 200 mg. acetylcarbromal, 125 and 250 mg. glutethimide, 400 mg. meprobamate and 5 mg. prochlorperazine. After an interview at which the type, symptoms and severity of the anxiety state were recorded, each subject was given a sufficient supply of any of the medications to last until his next visit to the clinic. The patient was advised to take 1 tablet three or four times daily. Such therapy was continued uninterrupted for not less than two weeks and usually for three weeks or longer. Since daytime sedation is a problem of chronic administration, it is important to continue evaluation of these agents under conditions of actual requirement. Multiple comparative trials were made in over half the study group. Twenty-three patients received four or more different drugs. One patient received all medications.

Daytime anxiety and associated insomnia, when present, were treated with multiple daytime doses only. No supplementary nighttime dose was used. An effort was made to determine if the anxiety factors which play a role in disturbances of sleep are affected by multiple daytime doses given to control daytime anxiety. Such a regimen might have advantages, since it would be possible to avoid potent sedative agents, which, in addition to a hypnotic effect, might result in a hang-over or other manifestations of prolonged action.

The response was rated according to rigid "all or none" criteria of efficacy. This permits direct application of results to everyday clinical practice in which the average patient and his physician regard anything less than complete relief as a failure. A satisfactory response required complete sustained relief without occurrence of untoward reactions for (1) daytime sedation, (2) nighttime hypnosis by small, frequent, daily doses, and (3) combined daytime sedation and nighttime hypnosis when both daytime anxiety and insomnia existed simultaneously. The response was considered satisfactory only if the patient's complaints were controlled throughout the entire period of drug administration. A response was considered unsatisfactory if tolerance or cumulative toxicity occurred despite an immediate effective response.

We also considered the response in terms of a therapeutic index—per cent effectiveness: per cent untoward reactions. This was considered as a guide which paralleled clinical needs. An occasional patient manifested excessive drowsiness which interfered with daytime activity. Although this was undoubtedly a sedative response, it was considered excessive for

TABLE 2

COMPARATIVE EFFECTIVENESS OF SEDATIVES IN PRODUCING A NIGHTTIME HYPNOTIC EFFECT WITH MULTIPLE DAYTIME DOSES

| MEDICATION | DOSE (*Three or four times daily*) | NUMBER OF PATIENTS | SATISFACTORY HYPNOTIC EFFECT WITH DAYTIME DOSAGE | | UNTOWARD REACTIONS (*Per cent*) | THERAPEUTIC INDEX* |
|---|---|---|---|---|---|---|
| | | | *Number of patients* | *Per cent* | | |
| Placebo | 1 tablet | 42 | 10 | 23.8 | 12.4 | 1.9 |
| Phenobarbital | 15 mg. | 24 | 12 | 50.0 | 30.0 | 1.6 |
| | 30 mg. | 19 | 13 | 68.4 | 35.0 | 1.9 |
| Acetylcarbromal | 200 mg. | 28 | 14 | 50.0 | 21.4 | 2.3 |
| Butabarbital sodium | 15 mg. | 35 | 21 | 60.0 | 10.0 | 6.0 |
| | 30 mg. | 50 | 26 | 52.0 | 16.4 | 3.1 |
| Glutethimide | 125 mg. | 17 | 6 | 35.3 | 15.6 | 2.2 |
| | 250 mg. | 28 | 13 | 46.4 | 50.0 | 0.9 |
| Meprobamate | 400 mg. | 31 | 17 | 54.9 | 26.5 | 2.0 |
| Prochlorperazine | 5 mg. | 33 | 10 | 30.0 | 20.0 | 1.5 |

*Per cent effectiveness: per cent untoward reactions.

TABLE 3

COMPARATIVE EFFECTIVENESS OF SEDATIVES IN PRODUCING COMBINED DAYTIME SEDATION AND A NIGHTTIME HYPNOTIC EFFECT WITH MULTIPLE DAYTIME DOSES

| MEDICATION | DOSE (*Three or four times daily*) | NUMBER OF PATIENTS | SATISFACTORY COMBINED DAYTIME SEDATION AND HYPNOTIC EFFECT | | UNTOWARD REACTIONS (*Per cent*) | THERAPEUTIC INDEX* |
|---|---|---|---|---|---|---|
| | | | *Number of patients* | *Per cent* | | |
| Placebo | 1 tablet | 36 | 9 | 25.0 | 12.4 | 2.0 |
| Phenobarbital | 15 mg. | 24 | 11 | 45.8 | 30.0 | 1.5 |
| | 30 mg. | 19 | 12 | 63.1 | 35.0 | 1.8 |
| Acetylcarbromal | 200 mg. | 28 | 13 | 46.4 | 21.4 | 2.1 |
| Butabarbital sodium | 15 mg. | 35 | 21 | 60.0 | 10.0 | 6.0 |
| | 30 mg. | 48 | 24 | 50.0 | 16.4 | 3.0 |
| Glutethimide | 125 mg. | 17 | 6 | 35.3 | 15.6 | 2.2 |
| | 250 mg. | 25 | 9 | 36.0 | 50.0 | 0.7 |
| Meprobamate | 400 mg. | 30 | 11 | 36.6 | 26.5 | 1.3 |
| Prochlorperazine | 5 mg. | 32 | 10 | 31.2 | 20.0 | 1.5 |

*Per cent effectiveness: per cent untoward reactions.

daytime sedation and was classified as an untoward reaction. The therapeutic index reflects the medication's clinical usefulness rather than its sedative action.

### *Results*

The comparative effectiveness of the daytime sedatives studied is summarized in table 1. A satisfactory sedative effect was obtained with multiple daytime doses of 15 and 30 mg. phenobarbital, 200 mg. acetylcarbromal, 15 and 30 mg. butabarbital sodium, and 125 mg. glutethimide. Cumulative untoward reactions, such as excessive daytime drowsiness, dizziness, mental sluggishness and memory disturbance, occurred with all drugs tested, except the doses of 15 mg. butabarbital sodium and 125 mg. glutethimide. For clinical usefulness, as reflected in the therapeutic index, both of these are satisfactory daytime sedatives. The ataractic drugs meprobamate and prochlorperazine were not satisfactory daytime sedatives according to the ideal criteria demanded of such medications.

The effectiveness of sedative agents in producing a nighttime hypnotic effect by means of

small multiple daytime doses is summarized in table 2. This was achieved satisfactorily without morning hang-over with doses of 15 and 30 mg. phenobarbital, 200 mg. acetylcarbromal, 15 and 30 mg. butabarbital sodium and 400 mg. meprobamate. However, with the exception of butabarbital sodium, the cumulative untoward reactions noted previously interfered with this hypnotic effect.

Table 3 presents the results of our study on the possibility of simultaneously controlling daytime anxiety and nighttime insomnia, when present together, by small daytime doses of sedative agents. This effect was achieved only with 30 mg. doses of phenobarbital and 15 and 30 mg. doses of butabarbital sodium. However, even the 30 mg. dose of phenobarbital was counterbalanced by a high incidence of untoward reactions.

In table 4 the various medications studied as daytime sedatives are rated according to their therapeutic index, which reflects clinical usefulness and not whether they are sedatives per se. In each of the categories studied, the dose of 15 mg. butabarbital sodium is rated first. The higher dose of 30 mg. butabarbital sodium is rated second in two categories, while glutethimide is satisfactory as a daytime sedative only. All other preparations are unsatisfactory either because of inadequate sedative action or because this action is counterbalanced by cumulative untoward reactions.

### *Discussion*

The confusion that exists in the field of daytime sedation and tranquilizing medications has been recently emphasized in a report of the Council on Drugs of the American Medical Association.[1] The method followed in the present study was used in an attempt to eliminate some of this confusion.

The practicing physician has been overwhelmed by the numerous so-called sedative agents, such as tranquilizers, calmatives or normalizers, which possess a sedative effect only on the basis of an overlapping pharmacologic action. Those agents that influence mental behavior by a specific "sedative" action on the central nervous system should be tested clinically under conditions the average

TABLE 4

COMPARATIVE RATING OF DAYTIME SEDATIVE AGENTS ACCORDING TO THERAPEUTIC INDEX*

| RATING | DAYTIME SEDATION | | | NIGHTTIME HYPNOTIC EFFECT WITH DAYTIME DOSAGE | | | COMBINED DAYTIME SEDATION AND NIGHTTIME HYPNOTIC EFFECT WITH DAYTIME DOSAGE | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Medication* | *Dose* (Three or four times daily) | *Index* | *Medication* | *Dose* (Three or four times daily) | *Index* | *Medication* | *Dose* (Three or four times daily) | *Index* |
| 1 | Butabarbital sodium | 15 mg. | 6.5 | Butabarbital sodium | 15 mg. | 6.0 | Butabarbital sodium | 15 mg. | 6.0 |
| 2 | Glutethimide | 125 mg. | 4.2 | Butabarbital sodium | 30 mg. | 3.1 | Butabarbital sodium | 30 mg. | 3.0 |
| 3 | Butabarbital sodium | 30 mg. | 3.3 | Acetylcarbromal | 200 mg. | 2.3 | Glutethimide | 125 mg. | 2.2 |
| | | | | Glutethimide | 125 mg. | 2.2 | Acetylcarbromal | 200 mg. | 2.1 |
| | | | | Meprobamate | 400 mg. | 2.0 | Placebo | 1 tablet | 2.0 |
| 4 | Placebo | 1 tablet | 2.5 | Phenobarbital | 30 mg. | 1.9 | Phenobarbital | 30 mg. | 1.8 |
| | Acetylcarbromal | 200 mg. | 2.5 | Placebo | 1 tablet | 1.9 | Prochlorperazine | 5 mg. | 1.5 |
| | Phenobarbital | 15 mg. | 2.0 | Phenobarbital | 15 mg. | 1.6 | Phenobarbital | 15 mg. | 1.5 |
| | Phenobarbital | 30 mg. | 2.0 | Prochlorperazine | 5 mg. | 1.5 | Meprobamate | 400 mg. | 1.3 |
| 5 | Prochlorperazine | 5 mg. | 1.9 | Glutethimide | 250 mg. | 0.9 | Glutethimide | 250 mg. | 0.7 |
| | Meprobamate | 400 mg. | 1.3 | | | | | | |
| 6 | Glutethimide | 250 mg. | 0.7 | | | | | | |

*Per cent effectiveness: per cent untoward reactions.

physician encounters in general practice before they are recommended as daytime sedatives. This also holds true for all medications which might have some sedative effect, regardless of their primary pharmacologic action. Thus, it is necessary to establish "ideal" criteria for a daytime sedative and to determine how closely standard and accepted daytime sedative agents meet these requirements. Placebo testing under similar conditions reflects the significance of method. Establishing effectiveness and incidence of untoward reactions with standard sedatives furnishes a yardstick with which all preparations recommended for control of anxiety states may be compared. The question always arises as to what should be the standard medication. Very often this is a widely used preparation which has been accepted without qualification; yet when studied under conditions demanded of the ideal, it falls far short. This is the case with phenobarbital. Nevertheless, controlled studies must include such medications, not because they are ideal but because of their widespread clinical use.

Daytime sedatives, although frequently used only occasionally, are more often recommended for chronic administration. Practical reasons demand that these medications be studied under such circumstances. The possible occurrence of tolerance, habituation and addiction, and of cumulative toxicity is more important to the physician and patient than is the observation of sedative action. Numerous toxic manifestations, which have been documented in the literature and noted by us, should be given due consideration when one is choosing sedative agents. A brief review of these manifestations is given in table 5. Elderly and debilitated patients are particularly sensitive to sedatives. Primarily because of decreased metabolism and impaired liver and kidney function, cumulative toxicity is not unusual. We are particularly concerned with the occurrence of mental confusion, bizarre neurologic complications, and antidiuretic effects. The latter have been noted particularly for phenobarbital and *Rauwolfia* alkaloids, but may occur with other drugs as their usage increases.

TABLE 5

TOXIC MANIFESTATIONS PRODUCED BY SEDATIVE AGENTS[2-52]

1. Skin manifestations*
   a. Exfoliative dermatitis—phenobarbital
   b. Exanthematous eruptions*—phenobarbital, meprobamate, butabarbital sodium, glutethimide, phenothiazine derivatives, acetylcarbromal
   c. Urticaria* (angioneurotic edema)—meprobamate, phenothiazine derivatives, glutethimide, phenobarbital, butabarbital sodium
   d. Photosensitivity—phenothiazine derivatives
   e. Purpura*—phenobarbital, meprobamate, butabarbital sodium, acetylcarbromal
2. Disturbances of the liver
   a. Hepatitis (parenchymatous)—phenobarbital
   b. Jaundice* (obstructive)—chlorpromazine
3. Disturbances of the kidneys*
   a. Antidiuretic* (production of edema, inhibition of diuretics)—phenobarbital, reserpine
   b. Nitrogen retention*—phenobarbital, reserpine
4. Blood dyscrasias
   a. Agranulocytosis—phenobarbital, chlorpromazine
   b. Megaloblastic anemia—phenobarbital
   c. Thrombopenic purpura—phenobarbital
   d. Aplastic anemia—meprobamate
5. Gastrointestinal disturbances*
   a. Peptic ulcer activation*—reserpine
   b. Persistent nausea and vomiting—chlorpromazine, meprobamate, glutethimide, phenobarbital, acetylcarbromal
   c. Diarrhea*—reserpine, chlorpromazine, meprobamate
6. Disturbances of the central nervous system*
   a. Toxic psychosis*—phenobarbital, glutethimide, acetylcarbromal, chlorpromazine, reserpine
   b. Extrapyramidal manifestations*—phenobarbital, chlorpromazine, reserpine
   c. Neurologic dysfunction* (paresis, palsy of extraocular muscles, cerebellar disturbances)—phenobarbital, reserpine, chlorpromazine
7. Disturbances of the autonomic nervous system*—reserpine, chlorpromazine, meprobamate
8. Cardiovascular disturbances*—barbiturates, chlorpromazine, reserpine
9. Addiction* (physical dependency)—barbiturates, glutethimide

*Observed personally.

Daytime symptoms of anxiety were accompanied by insomnia in approximately 70 per cent of the patients treated. Three clearly defined types of insomnia—inability to fall asleep, an interrupted sleep pattern, and an insufficient duration of sleep—were noted.

Evaluation of the effectiveness of daytime sedatives in controlling nighttime insomnia has indicated several interesting features. Control of daytime symptoms of the anxiety state does

*Per cent effectiveness; per cent untoward reactions.

not necessarily mean that the coexistent insomnia will also be alleviated. Apparently there may be a dissociation of effect. A satisfactory daytime sedative such as glutethimide requires supplementary hypnotic medication. On the other hand, if it were possible to control daytime anxiety and insomnia with small daytime doses of a sedative agent, such an effect would have decided advantages. It would thus be possible to avoid morning hang-over, mental sluggishness and lethargy. Control of both daytime and nighttime symptoms of anxiety by a single medication, without recourse to additional therapy, has been noted in this study only with butabarbital sodium.

We have tried to emphasize certain features of sedative therapy which approach the actual utilization of these medications in practice. It is not enough to state that a medication is an acceptable sedative unless it is also known what cumulative toxic manifestations might result with its use. Sedation with excessive drowsiness or persistent nausea or vomiting is not a satisfactory response since these untoward reactions interfere with clinical effectiveness. The therapeutic index as defined in this study reflects clinical usefulness and indicates to what degree a sedative agent approaches the ideal.

### *Conclusions*

1. Sedative agents should be evaluated under conditions of actual clinical practice, and the responses should be rated with reference to standard and placebo therapy according to "ideal" criteria.

2. Although daytime anxiety and nighttime insomnia may be separate problems, it is possible to relieve both by means of small multiple daytime doses of effective sedatives.

3. Butabarbital sodium provided the highest rating (therapeutic index) of sedatives studied for control of anxiety and insomnia by daytime dosage.

4. Glutethimide in small doses is an effective daytime sedative, but supplementary hypnotic doses are required to control insomnia.

5. Phenobarbital and acetylcarbromal will produce satisfactory daytime sedation. However, chronic administration of these drugs will produce a high incidence of cumulative toxicity.

6. Meprobamate and prochlorperazine, representative ataractic drugs, are not satisfactory daytime sedatives according to the "ideal" criteria demanded of such medications.


### ACKNOWLEDGMENT

The authors acknowledge the assistance of the following pharmaceutical companies which participated with generous supplies of medications or grants-in-aid: Bristol Laboratories Inc.; Ciba Pharmaceutical Products, Inc.; Lederle Laboratories Division, American Cyanamid Company; Thos. Leeming & Co., Inc.; McNeil Laboratories, Inc.; Pfizer Laboratories, Division, Chas. Pfizer & Co., Inc.; Wallace Laboratories; Warner-Chilcott Laboratories; Winthrop Laboratories; Wyeth Laboratories.


### REFERENCES


1. Report of Council on Drugs: Psychotherapeutic drugs. J.A.M.A. 166:1040 (March 1) 1958.
2. Alexander, L. H.: Reactions With Drug Therapy. Philadelphia, W. B. Saunders Company, 1955.
3. Beckman, H.: Pharmacology in Clinical Practice. Philadelphia, W. B. Saunders Company, 1952.
4. Goodman, L. S. and Gilman, A.: The Pharmacological Basis of Therapeutics. Ed. 2. New York, The Macmillan Company, 1956.
5. Osol, A. and Farrar, G. E.: The Dispensatory of the United States of America. Philadelphia, J. B. Lippincott Company, 1950.
6. Pijoan, M. and Yaeger, H. C.: A Handbook of Commonly Used Drugs. Springfield, Illinois, Charles C Thomas, 1947.
7. Brown, A. E.: Drug allergy. Quart. Rev. Allergy 7:51 (March) 1953.
8. Tatum, A. L.: The present status of the barbiturate problem. Physiol. Rev. 19:472 (October) 1939.
9. Isbell, H.: Addiction to barbiturates and barbiturate abstinence syndrome. Ann. Int. Med. 33:108 (July) 1950.
10. Welton, D. G.: Exfoliative dermatitis and hepatitis due to phenobarbital. J.A.M.A. 143:232 (May 20) 1950.
11. Boos, E. P. and Erf, L. A.: Thrombocytopenic purpura following medication with Sedormid and with phenobarbital. New York J. Med. 36:491 (April) 1936.
12. Hadler, A. J.: Granulocytopenia following barbiturate therapy. New England J. Med. 222:755 (May) 1940.
13. Watkins, C. H.: The possible role of barbiturates and amidopyrine in the causation of leukopenic states. Proc. Staff Meet. Mayo Clin. 8:713, 1933.
14. Brodwall, E. and Stöa, K. F.: A study of barbiturate clearance. Acta med. scandinav. 154:139, 1956. Abstracted in J.A.M.A. 161:1104 (July 14) 1956.
15. Kreindler, A. and Cohen, E.: Ueber seltene Komplikationen der Luminaltherapie. München. med. Wchnschr. 77:1844 (October 24) 1930.
16. Potter, J. K. and Whitacre, R. J.: Dermatitis due to barbiturates: Report of a case with associated

anemias. Ann. Int. Med. 21:1041 (December) 1944.
17. Menninger, W. C.: Skin eruptions from phenobarbital. J.A.M.A. 91:14 (July) 1928.
18. McGeachy, T. E. and Bloomer, W. E.: Phenobarbital, sensitivity syndrome. Am. J. Med. 14:600 (May) 1953.
19. Sneddon, I. B. and Leishman, A. W. D.: Severe and fatal phenobarbitone eruptions. Brit. M. J. 1:1276 (June) 1952.
20. Isbell, H.: Addiction to analgesics and barbiturates. Pharmacol. Rev. 2:355, 1950.
21. De Bodo, R. C. and Prescott, K. F.: The antidiuretic action of barbiturates (phenobarbital, Amytal, pentobarbital) and the mechanism involved in this action. J. Pharmacol. & Exper. Therap. 85:222 (November) 1945.
22. Isbell, H.: Acute and Chronic Barbiturate Intoxication. Washington, D.C., Veterans Administration Technical Bulletin 10-76, August 15, 1951.
23. Friedman, H. T. and Marmelzat, W. L.: Adverse reactions to meprobamate. J.A.M.A. 162:628 (October 13) 1956.
24. Selling, L. S.: Clinical study of a new tranquilizing drug. J.A.M.A. 157:1594 (April 30) 1955.
25. Kositchek, R. J.: Reactions to meprobamate. J.A.M.A. 161:644 (June 16) 1956.
26. Queries and Minor Notes: Allergic reaction to meprobamate. J.A.M.A. 163:795 (March 2) 1957.
27. Carmel, W. J., Jr. and Dannenberg, T.: Nonthrombocytopenic purpura due to Miltown (2-methyl-2-N-propyl-1, 3-propanediol dicarbamate). New England J. Med. 255:770 (October) 1956.
28. Karlinsky, W.: Allergic purpura due to meprobamate. Canad. M.A.J. 74:1012 (June) 1956.
29. Meyer, L. M., Heeve, W. L. and Bertscher, R. W.: Aplastic anemia after meprobamate therapy. New England J. Med. 256:1232 (June) 1957.
30. Falk, M. S.: Allergic reaction to meprobamate. A.M.A. Arch. Dermat. 75:437 (March) 1957.
31. Lemere, F.: Habit-forming properties of meprobamate (Miltown or Equanil). A.M.A. Arch. Neurol. & Psychiat. 76:205 (August) 1956.
32. Stroud, G. M.: Drug eruptions due to meprobamate. New England J. Med. 256:354 (February) 1957.
33. Special Reports: Potential hazards of meprobamate. J.A.M.A. 164:1332 (July 20) 1957.
34. Wrong, N. M.: Purpuric eruption due to Sedicin. Canad. M.A.J. 68:591 (June) 1953.
35. Morawitz, B. V. P.: Abasim-Gebrauch, lang da nernder, als Ursache einer hämorrhagischen Diathese unter dem Bilde der Purpura Majocchi. Sammlung von Vergiftungsfällen 2:71 (May) 1931.
36. Weston, D. T.: Treating insomnia with Doriden, a new nonbarbiturate sedative. Journal-Lancet 76:1 (January) 1956.
37. Davis, C. A. and Gruener, R. D.: Glutethimide—a new nonbarbiturate hypnotic. California Med. 84:290 (April) 1956.
38. Stein, A. A. and Wright, A. W.: Hepatic pathology in jaundice due to chlorpromazine. J.A.M.A. 161:508 (June 9) 1956.
39. May, R. H. and Voegele, G. E.: Parkinsonian reactions following chlorpromazine and reserpine: Similar reactions in the same patients. A.M.A. Arch. Neurol. & Psychiat. 75:522 (May) 1956.
40. Dickel, H. A. and Dixon, H. H.: Inherent dangers in use of tranquilizing drugs in anxiety states. J.A.M.A. 163:422 (February) 1957.
41. Adams, J. C. L., Corti, K. D. F. and Hobson, Q. J. G.: Agranulocytosis and severe leucopenia after chlorpromazine hydrochloride. Brit. M. J. 1:1087 (May) 1956.
42. Goldman, D.: The major complications of treatment of psychotic states with chlorpromazine and reserpine and their management. In Psychiatric Research Report No. 4. Washington, D.C., American Psychiatric Association, April 1956, p. 79.
43. Miner, R. W. (ed.): Reserpine (Serpasil) and other alkaloids of *Rauwolfia serpentina*: Chemistry, pharmacology and clinical applications. Ann. New York Acad. Sc. 59:1-140 (April) 1954.
44. Sarwer-Foner, G. J. and Ogle, W.: Psychosis and enhanced anxiety produced by reserpine and chlorpromazine. Canad. M.A.J. 74:526 (April) 1956.
45. Lemieux, G., Davignon, A. and Genest, J.: Depressive states during *Rauwolfia* therapy for arterial hypertension: A report of 30 cases. Canad. M.A.J. 74:522 (April) 1956.
46. Margolis, L. H.: Pharmacotherapy in psychiatry; a review. Ann. New York Acad. Sc. 66:698, 1957.
47. Report of Council on Drugs: Blood dyscrasias associated with promazine hydrochloride therapy. J.A.M.A. 165:685 (October 12) 1957.
48. Queries and Minor Notes: Chlorpromazine jaundice. J.A.M.A. 163:1660 (April 27) 1957.
49. Cohen, I. M.: Complications of chlorpromazine therapy. Am. J. Psychiat. 113:115 (August) 1956.
50. Ayd, F. J.: New pharmacotherapeutic drugs for psychic disturbances. Current M. Digest 23:59 (October) 1956.
51. Foreign Letters: Tranquilizers. J.A.M.A. 165:1472 (November 16) 1957.
52. Epstein, J. H., Brunsting, L. A., Petersen, M. C. and Schwarz, B. E.: A study of photosensitivity occurring with chlorpromazine therapy. J. Invest. Dermat. 28:329 (May) 1957.

SYMPOSIUM

# Diagnosis and Treatment of Pancreatitis

ROBERT M. ZOLLINGER,[1] EDWIN H. ELLISON,[2] DAN W. ELLIOTT,[3] STANLEY O. HOERR[4] AND WILLIAM D. HOLDEN[5]

DR. ROBERT M. ZOLLINGER (Moderator): Symptoms of acute pancreatitis are bizarre and at times defy accurate diagnosis, and recently more and more patients have been found to have chronic forms of pancreatitis. I am not sure anyone knows much about this disease, but we will try to find out what we can in this discussion.

ROBERT M. ZOLLINGER

### *Symptoms of Acute Pancreatitis*

Dr. Holden, what symptoms lead you to suspect that a patient has acute pancreatitis?

[1]Professor and Chairman, Department of Surgery, Ohio State University College of Medicine, Columbus, Ohio.

[2]Professor and Chairman, Department of Surgery, Marquette University School of Medicine, Milwaukee, Wisconsin.

[3]Assistant Professor of Surgery, Ohio State University College of Medicine, Columbus, Ohio.

[4]Professor of Surgery and Chairman, Division of Surgery, The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

[5]Oliver H. Payne Professor of Surgery, Western Reserve University School of Medicine, Cleveland, Ohio.

Presented before the forty-third annual Assembly of the Interstate Postgraduate Medical Association at Cleveland.

DR. WILLIAM D. HOLDEN: The main symptom of acute pancreatitis, whether it is the so-called acute edematous or interstitial pancreatitis, or acute hemorrhagic pancreatic necrosis, is abdominal pain. The manifestations of this disease are innumerable, and it can mimic almost any other abdominal disorder. In mild cases the pain usually is confined to the upper portion of the abdomen, and the typical area of referral is in the midportion of the back between the scapulae; it may be on one side or the other, or it may have a central distribution. The pain is somewhat characteristic in that it is deep-seated, rather constant, and dull in the mild cases. In the more severe cases it is extremely intense. Attacks frequently are associated with ingestion of a heavy meal or a large quantity of alcohol.

DR. ZOLLINGER: I had hoped you wouldn't say that.

DR. HOLDEN: It is true. This sometimes gives a lead to the nature of the problem. Vomiting is variable; some patients do not vomit and others have intense retching, even though the first emesis empties the stomach completely. The severity of this disease may lead very rapidly to hypotension and tachycardia, sometimes in a matter of hours. This picture is not characteristic, however, in contrast to the

EDWIN H. ELLISON

DAN W. ELLIOTT

STANLEY O. HOERR

WILLIAM D. HOLDEN

statements in some textbooks; it is relatively uncommon. After a period of 24 hours this picture may be much more characteristic of acute pancreatic necrosis, but early in the disease process it is not typical.

DR. ZOLLINGER: What about the textbook picture of bandlike pain and an ashen color? Is this typical?

DR. HOLDEN: Bandlike pain is very unusual.

DR. ZOLLINGER: Can involvement of localized areas of the pancreas give rise to pain, say, in the left upper quadrant and the right upper quadrant?

DR. HOLDEN: Yes, I think that is true. Occasionally one sees a patient who from the standpoint of clinical evaluation appears to have characteristic acute cholecystitis and in whom one finds a completely normal biliary tree and pancreatitis, generally confined to the head. This is not true for most patients, in that pancreatitis is a diffuse disease.

DR. ZOLLINGER: Are you seeing more cases of pancreatitis now than you did formerly?

DR. HOLDEN: I think we see more. Everyone is more aware of it, and we are now recognizing as pancreatitis episodes of mild abdominal pain and a fever for one or two days; formerly we might have called them gastritis or might not have known the cause.

### *Value of Amylase Determinations*

DR. ZOLLINGER: Dr. Hoerr, can you make a diagnosis of pancreatitis on the basis of the history and physical examination or do you need amylase determinations?

DR. STANLEY O. HOERR: I need amylase determinations. I think they are valuable.

DR. ZOLLINGER: Do you make amylase determinations in every case of abdominal pain, or is that an extreme?

DR. HOERR: I think it is a little extreme. Sometimes one can tell that a patient has acute appendicitis or strangulated hernia—

DR. ZOLLINGER: I thought appendicitis was the hardest diagnosis in the world for a physician to make.

DR. HOERR: It can be, but sometimes it is relatively clear, and an amylase test is a waste of time in such a case.

DR. ZOLLINGER: Do you mean if the abdominal pain is a little vague and not classic of acute appendicitis you would run an amylase test?

DR. HOERR: Yes.

DR. ZOLLINGER: Would you do it in the middle of the night?

DR. HOERR: Yes.

DR. ZOLLINGER: On a man who had been in an automobile accident and had been hit in the epigastrium with a steering wheel?

DR. HOERR: I might, but I would be inclined to consider operating or not operating on that patient for reasons other than a high or a low amylase level.

DR. ZOLLINGER: Would you order the test if you thought that the patient had acute cholecystitis?

DR. HOERR: Yes, but I would be inclined to operate even if he had a high amylase; however, it is valuable information. I have seen patients with acute cholecystitis and a high amylase level, as I am sure you have, and it would be a mistake not to operate and either decompress or remove the gallbladder just because you thought that they had an associated pancreatitis.

DR. ZOLLINGER: Do you believe that a physician practicing in a community with a small hospital should make an issue of the availability of amylase determinations, day or night?

DR. HOERR: He probably should. At our institution we have a method to determine the amylase level which has proved quite useful. It is a test which determines whether the amylase is above or below 600 units.

DR. ZOLLINGER: That is normal?

DR. HOERR: No, but we have arbitrarily selected that level as significant.

DR. ZOLLINGER: Is this test practical for the small hospital laboratory?

DR. HOERR: It was set up by the clinical pathologist so that no titration or determination of the blood sugar is necessary.

DR. ZOLLINGER: You have to have a laboratory technician available in the hospital to run the test.

DR. HOERR: You have to have someone who knows how to do the test. I don't know how, but I think I could learn in probably 10 or 15 minutes. And if we did not have someone to do it, I would learn. I believe that this is a valuable test.

DR. ZOLLINGER: How many physicians in the audience do not have amylase determinations available to them at night? (The majority.) Dr. Hoerr, you should write a paper on the method, since there appears to be a need for such a simplified test.

How many of the panel members would put as much reliance on amylase elevations as on a leukocyte count? (All of them.) The audience does not always have amylase determinations available, so we will wait for Dr. Hoerr's easy method. You may have to fight with the pathologist or your laboratory technicians to make this test available. There are rather quick methods available today, and I think if you make an issue of it you might have this test. It is very worthwhile.

### *Peritoneal Tap*

DR. HOLDEN: We ought to say here that a normal amylase in no way eliminates a diagnosis of pancreatitis.

DR. ZOLLINGER: Dr. Ellison, what if the amylase is normal and the patient still has abdominal pain?

DR. EDWIN H. ELLISON: When the blood amylase is normal in patients suspected of having an attack of acute pancreatitis, we turn to another diagnostic aid, a peritoneal tap.

DR. ZOLLINGER: How do you do that?

DR. ELLISON: The peritoneal tap is a relatively simple procedure. Having assured yourself that the patient's bladder is empty and with the patient in a semisitting position, an 18 gauge needle attached to a 10 or 20 cc. syringe can quite easily be inserted into the peritoneal cavity. If the patient has not had previous abdominal operations, the paracentesis is accomplished in the midline at or about the junction of the upper and middle thirds of the space between the umbilicus and the pubis. As the needle passes through the peritoneum one feels a definite "give" or "twang." Suction is then applied to the syringe. The small amount of characteristic yellowish blood-tinged fluid obtained in patients with pancreatitis will have a markedly elevated amylase as long as five to seven days after onset of the disease.

DR. ZOLLINGER: What if you get only 0.5 or 1 cc. of fluid?

DR. ELLISON: That amount is quite sufficient. In the original report of the method, Keith found that the amylase frequently was so high that a tenfold dilution was necessary before the amylase values could be measured by standard methods. This procedure is most helpful, since the amylase remains elevated for as long as five to seven days. The serum amylase may return to normal within 24 hours of onset of the acute process.

DR. ZOLLINGER: When you were at our institution you were afraid to do this and had the interns do it. Do you have more confidence since you have moved to Milwaukee?

DR. ELLISON: I recall doing a peritoneal tap in a few cases in my earlier days. At least I gained sufficient know-how to be able to demonstrate its simplicity to the house staffs in Milwaukee.

DR. ZOLLINGER: What about the danger of sticking a needle in the peritoneal cavity?

DR. ELLISON: The bowel falls away in front

of the needle. If you are fearful of perforating the intestine, a stylet can be used in the needle.

DR. ZOLLINGER: Maybe you think the patient has a perforated ulcer; how are you going to tell whether he has a mesenteric thrombosis or a perforated ulcer?

DR. ELLISON: An amylase test alone is not sufficient. There are other tests one can make on the peritoneal fluid which are quite helpful. Bile should be looked for and, if present, a perforation must be suspected somewhere in the gastrointestinal tract.

DR. ZOLLINGER: Or else the needle went into the bowel.

DR. ELLISON: I recall an instance when you thought I had inserted the needle in the bowel but the patient had a ruptured gallbladder.

DR. ZOLLINGER: I remember that case. I thought Dr. Ellison had been aspirating the jejunum by the syringe. I am not sure yet that he wasn't.

DR. ELLISON: There are other things to be checked out. The fluid from a patient with perforated ulcer frequently will be a clear yellow but will often contain flakes of fibrin or perhaps even food particles. Further, and perhaps even more diagnostic, air is obtained when the needle first enters the peritoneal cavity. Gas from the bowel would, of course, have a fecal odor.

DR. ZOLLINGER: Have you had much experience with or confidence in looking for fat globules under the microscope to diagnose pancreatitis?

DR. ELLISON: We always discussed this finding, but I have never really been too impressed with the fat globules.

DR ZOLLINGER: It probably is a waste of time. However, the peritoneal tap is worthwhile. I see the young men using it more and more. Gynecologists use it to see whether there is blood in the pelvis. Our young men use it constantly when there is a question of blood in the peritoneal cavity from a ruptured spleen associated with an automobile accident. Finally, it is very useful in checking for peritoneal amylase elevation, because, as Dr. Ellison said, these amylase levels remain high for six or seven days after the blood levels have returned to normal.

### *X-ray Examination*

Dr. Elliott, how valuable is the x-ray in the diagnosis of pancreatitis?

DR. DAN W. ELLIOTT: X-rays are valuable principally to help rule out other causes of upper abdominal pain. Of course one looks for free air in the abdomen, which is indicative of a perforated viscus, and for evidence of mechanical obstruction of the small bowel.

DR. ZOLLINGER: I thought paralytic ileus and small bowel obstruction were associated with pancreatitis.

DR. ELLIOTT: The findings of pancreatitis itself are simply those suggesting an irritative process in the abdomen, that is, some degree of paralytic ileus. There also may be some distention of the colon. There is nothing else in the x-ray that is characteristic of pancreatitis by itself. A few things direct suspicion to the pancreas, one of them being pleural effusion on the left side.

DR. ZOLLINGER: How do you explain pleural effusion on the left side in pancreatitis?

DR. ELLIOTT: Probably it is due to irritation just below the diaphragm. It certainly is more commonly seen on the left than on the right side, and it is not an infrequent finding in acute pancreatitis.

DR. ZOLLINGER: What other signs do you look for?

DR. ELLIOTT: One can look for evidence of calcium in the pancreas. This will be evident only rarely during acute pancreatitis, perhaps in one case in 10, but it is helpful then. There is something wrong in the pancreas when there is calcification within the gland. Sometimes one can see opaque biliary calculi, and since gallstones are so commonly associated with acute pancreatitis this finding may be suggestive when the x-rays also show paralytic ileus.

DR. ZOLLINGER: To sum up what has been said about diagnosis of pancreatitis, when you have a patient who has abdominal pain which is somewhat baffling and you cannot make up your mind what it is, it is worthwhile to obtain a blood amylase determination in addition to a leukocyte count. A peritoneal tap for amylase determinations is worthwhile. One can search for gallstones or calcification within the

pancreas on x-rays of the abdomen, and a certain amount of paralytic ileus.

### *Treatment of Acute Pancreatitis*

Dr. Holden, how do you treat acute pancreatitis? Should these patients have operative treatment?

DR. HOLDEN: The first thing we must realize is that this disease can be highly lethal. The mortality for pancreatic necrosis is still high, although when the disease is confined to the pancreas and proper treatment is instituted the mortality is quite reasonable. This disease places many demands on the body as a whole. Obviously the patient must be confined strictly to bed during the early stages of the acute process. Anything which activates the exocrine enzyme system of the pancreas must be inhibited insofar as this is possible. A practical and reasonably satisfactory means to do this is to give nothing by mouth, put a gastric tube in the pyloric canal, apply constant suction, and consistently give fairly large doses of atropine to minimize vagal activity and its effect on the enzyme production of the pancreas. The patient's pain must be relieved, and DEMEROL® is preferable to morphine, if it gives sufficient relief.

DR. ZOLLINGER: Do you think that really makes any difference?

DR. HOLDEN: Many times morphine is the only thing that will relieve the pain. Certainly we know that experimentally and theoretically it makes a difference. We know that in human beings if you give morphine you can raise intraductal pressure in the biliary tract, and there is reason to believe Demerol is less injurious in this disease than morphine may be.

DR. ZOLLINGER: Let us find out from the audience how many of them use Demerol for abdominal pain and how many use morphine rather routinely. The ratio is about 10 to 1 for Demerol. Those of you using morphine should remember that it may aggravate the pancreatitis.

### *Adequate Replacement Therapy; Control of Infection*

DR. HOLDEN: The next principle in the therapy of pancreatitis that must be appreciated is adequate replacement of the tremendous losses of fluids, electrolytes and protein from the blood and from the extracellular space into the inflamed area, whether it is within the pancreas, in the peripancreatic tissues, or throughout the peritoneal cavity. This requires, I think, an alertness on the part of the physician to overdo, if anything, replacement therapy rather than underdo it. Replacement therapy must consist of an adequate quantity of water, sodium, chloride (especially if gastric suction is being applied), potassium, and calcium if there is a marked depression of calcium.

DR. ZOLLINGER: Just a minute. You say *if* there is a marked depression of calcium. Would you give calcium on the first day of the attack before you knew the level, and, if so, how would you give it?

DR. HOLDEN: On the first day I would give 1 gm. of calcium gluconate anyway. It takes several hours to find out whether the calcium is going to be depressed. By the second morning one knows whether the calcium is 10 or 6.5, and then can administer more calcium if necessary.

DR. ZOLLINGER: Have you ever seen a patient recover who had a blood calcium of 6.5?

DR. HOLDEN: I don't think so, but I have seen them recover with 7.5.

DR. ZOLLINGER: That's getting pretty close to the line at 7.5.

DR. HOLDEN: There is a big difference.

Next one must realize that if the disease continues for any length of time there can be, and there frequently is, an overwhelming pyogenic infection of the pancreas and even the peritoneal cavity. Any one of a dozen organisms may be responsible, and usually there is a mixture. Generally they are gram-negative rods. Anaerobic bacilli may be present, such as Welch's bacilli. The gram-positive cocci may be involved in this process.

DR. ZOLLINGER: I don't understand, Dr. Holden, why you are so emphatic about infection. Where does this come from? Is it associated with dead tissue?

DR. HOLDEN: I don't know just how it gets there, but it is there, and I think the growth is enhanced because of the presence of dead

tissue. How these organisms get there is theoretical. They may come by way of the lymphatics from the intestinal tract, from the blood stream, or as direct invaders from the gastrointestinal tract through the biliary tree.

DR. ZOLLINGER: I never thought too much about infection in pancreatitis.

DR. ELLISON: It would be important to rule out an infection somewhere else. For example, if the patient were known to have acute tonsillitis he might be more prone to the development of an infectious complication.

DR. ZOLLINGER: How could you tell, if a stomach tube had been in place for two or three days, whether he had tonsillitis or irritation from the tube?

DR. ELLISON: Resort to the old-fashioned tongue blade.

DR. ELLIOTT: How many cases are infected?

DR. HOLDEN: I think relatively few. Twenty years ago a good many were. We would see the patients four or five days after the onset of the disease, or that is when we would make the diagnosis. We would operate, and would culture organisms out of the peritoneal cavity almost consistently. If a necrotic pseudocyst develops over a period of a week, almost invariably one can culture at least one organism out of it if you drain it during this stage, and frequently three or four organisms can be cultured. Even today, in fatal cases, frequently one can get coliform organisms and *Proteus*, sometimes Welch's bacilli, staphylococci, anaerobic streptococci, and all sorts of organisms. I do not mean that the patient ends up with a massive pyogenic infection or a pyogenic abscess, but these organisms are in this process and ultimately these patients can die with bacteremia or septicemia unless we realize this and intensify efforts to control the infection.

DR. ZOLLINGER: You are outlining an intensive treatment that is not a great deal different from that for a staphylococcic enterocolitis—lots of fluids, antibiotics, calcium, almost everything on the shelf.

DR. HOLDEN: That is about right.

DR. ZOLLINGER: Dr. Hoerr, what has been your experience? Maybe Dr. Holden gets the bad cases and you get the good ones.

DR. HOERR: I don't have much experience with primary acute pancreatitis. I have seen some bad cases postoperatively, I am sorry to say, and we follow a regimen much like that outlined by Dr. Holden. I think the two things we emphasize heavily are the corticosteroids and either blood plasma or albumin in massive doses. In the past couple of years we have had a couple of patients who would have been lost five or six years ago and who have recovered on this regimen.

I should like to ask a question about this calcium business. Far be it from me to decry the replacement of anything running low, but I wonder how much of a factor it is in making these patients sick. Isn't it more of an evidence of an overwhelming process than something dangerous in and of itself?

DR. ZOLLINGER: You don't see it depleted in many of the other overwhelming processes, do you?

DR. HOERR: You certainly see patients with calcium levels of 6 who get well, though.

DR. ZOLLINGER: Dr. Holden, here is a nice problem for you.

DR. HOLDEN: I don't know the real significance of the depression of calcium. I don't think I have ever seen anyone get into serious trouble because of a depressed calcium level per se in this disease.

DR. ZOLLINGER: Some people have said that tetany will develop in a number of patients with abdominal pain and pancreatitis. I have never seen it.

DR. HOLDEN: Nor have I.

DR. ELLISON: I have seen tetany in these patients. Another finding we have failed to mention is the development of hyperlipoidemia in many of these patients. I believe this results from the disease and is not a causative factor. Incidentally, the free ionized calcium may be much lower than the level obtained by a blood calcium determination, and tetany may result with the calcium seemingly normal.

DR. ZOLLINGER: I don't quite understand that. When there is pancreatitis there is a lot of fat floating around in the blood.

DR. ELLISON: Yes, in many instances.

DR. ZOLLINGER: What does that do to the calcium?

DR. ELLISON: The ionized calcium combines

with the free fatty acids to form a calcium salt.

DR. ZOLLINGER: Then there is practically a limestone blood.

DR. ELLISON: That is right.

DR. ZOLLINGER: And therefore the level is low and one finds that in a patient near death from pancreatitis the fat saturation is rising.

DR. ELLISON: It does in many instances. I believe if we measured the blood fatty acid levels in patients with pancreatitis we would find them to be elevated in many cases.

DR. HOLDEN: I want to add that I have seen patients who have had hyperactivity of the muscular system with pancreatitis, but every one has had a metabolic alkalosis because of the excessive removal of hydrochloric acid from the stomach and inadequate replacement of chloride. As soon as this is readjusted, these patients may have calcium levels of 10, not depressed at all. I have never seen a patient with a normal pH and a seriously depressed serum calcium in this disease.

DR. ELLISON: The blood calcium may also be elevated by an associated hyperparathyroidism. As I recall, some 15 cases of hyperparathyroidism associated with acute pancreatitis have been reported.

DR. ZOLLINGER: Dr. Elliott, you have studied this problem. Would you explain the type of intravenous fluid which you believe, based on experimental evidence, is important? Can you prove it has lowered the mortality rate?

DR. ELLIOTT: First, to clear up the question of calcium, I want to say that Dr. Mark Hayes at Yale did describe some cases in which tetany appeared, due to low calcium levels. He could better treat this by administering parathyroid hormone than he could with reasonable quantities of calcium. I think one should watch the patient with pancreatitis for the appearance of muscle irritation and of tetany. This calls for a check of the serum chlorides and the carbon dioxide-combining power, and for the administration of calcium.

DR. ZOLLINGER: Have you ever seen a case of tetany?

DR. ELLIOTT: We have seen some muscle irritability such as Dr. Holden described.

DR. ZOLLINGER: Have you ever seen a case of tetany?

DR. ELLIOTT: No, not one proved due to low calcium.

DR. ZOLLINGER: I want to know why and what type of intravenous fluid is important. When you ask this question of young men today, you find that everybody gets a bottle of salt and a bottle of glucose. Why shouldn't we stay routine as far as treating pancreatitis is concerned?

DR. ELLIOTT: Pancreatitis varies in severity from the very mildest—

DR. ZOLLINGER: This is a very bad case.

DR. ELLIOTT: Two-thirds of the cases are bad, and one can identify them almost at once by the presence of abdominal distention and paralytic ileus with vomiting.

DR. ZOLLINGER: Then the abdominal ileus worries you when you see it in a patient with pancreatitis.

DR. ELLIOTT: In pancreatitis, abdominal distention and persistent vomiting are signs of a severe process. Not only is the intravenous administration of water, glucose and salt indicated, but in addition we have routinely administered albumin or plasma. We have learned from direct measurements that in patients with abdominal distention, blood volume deficits develop very rapidly, averaging about 3 pt. of blood in the first 24 hours.

DR. ZOLLINGER: Where does that lost blood and plasma go?

DR. ELLIOTT: Almost entirely into the peritoneal cavity.

DR. ZOLLINGER: Is part of it lost into the bowel because there is distention?

DR. ELLIOTT: Probably the ileus also traps protein-rich fluid in the walls of the bowel; certainly there is fluid in the retroperitoneal tissues; there is marked swelling in the area of the pancreas itself; there is always some degree of ascites or ascitic fluid present.

DR. ZOLLINGER: Then you feel that every patient with acute pancreatitis that is severe, with abdominal distention, needs albumin, blood or plasma?

DR. ELLIOTT: Yes.

DR. ZOLLINGER: How many physicians in the audience have albumin available? (Quite a number.) How many feel it is too expensive to use? (Almost the same number.) How many

of the panelists believe that it has specific merit? (Two.)

DR. HOLDEN: Do you mean better than blood or plasma?

DR. ZOLLINGER: Yes, for this disease. Do you think it has a special antitryptic effect?

DR. ELLISON: No. I use it primarily for its osmotic effect. It works, as Dr. Elliott said.

DR. ZOLLINGER: He uses it because he gets it free; it is very expensive.

DR. ELLISON: Where we are, Uncle Sam and the county pay for it.

DR. ZOLLINGER: I am paying for it too if Uncle Sam is. Can't we use whole blood?

DR. ELLISON: It is hard to believe a patient needs whole blood when he has a hemoglobin of 15.5 or 16 gm. and a high hematocrit.

DR. ZOLLINGER: Doesn't hemolysis of the red cells occur in pancreatitis?

DR. ELLISON: Hemolysis will occur and may play some role in the anemia which develops some four or five days later with a hemoglobin of 9 gm.

DR. ZOLLINGER: Why not give blood?

DR. ELLISON: It should be obvious that patients with a high hemoglobin need plasma or a plasma expander.

DR. ZOLLINGER: You will settle for plasma?

DR. ELLISON: I will settle for plasma.

DR. HOLDEN: Why does the patient need plasma because he has a high hematocrit or a high hemoglobin? What he needs is water, if you are talking about just the relation of the hematocrit to fluid dynamics.

DR. ZOLLINGER: What about that idea, Dr. Elliott?

DR. ELLIOTT: Unquestionably such a patient needs water, but in addition he needs something to maintain this water within his circulation. His protein loss is demonstrably large. To maintain his circulation he needs protein, whether albumin or plasma.

DR. ZOLLINGER: Dr. Holden, what do you say to that?

DR. HOLDEN: This is perfectly true, but the principal osmotic effect that you can create, or replace when there is a deficit, is with electrolytes. It is true that these are lost from the blood stream rapidly, but so is protein in this diffuse inflammatory process. I think what Dr. Elliott said is important, that a few days later you find that the hemoglobin, which was 15 gm., is 9 gm., and this is one of the reasons we would prefer, at least initially, to use blood along with massive replacement of water and electrolytes.

DR. ZOLLINGER: I think Dr. Elliott has the idea that the colloids, blood, plasma or albumin, may be dehydrators of the acutely inflamed pancreas, similar to the effect of hypertonic solutions which have been administered to decrease intracranial pressure.

DR. ELLIOTT: We have some evidence of this. However, I do not think it is conclusive or that one has to use hypertonic albumin for this effect.

DR. ZOLLINGER: What if such solutions were not available—no blood, no plasma, nothing but dextran? Would you use it?

DR. ELLIOTT: Yes, I would.

DR. ZOLLINGER: Do you have experimental evidence that it is pretty good?

DR. ELLIOTT: Yes.

DR. ZOLLINGER: How many physicians in the audience have dextran available? (Quite a large number.) Well, if you are hard-pressed, in an acute condition, with distention, you may use dextran. Do you object to that, Dr. Holden?

DR. HOLDEN: I would use dextran if I did not have anything else available.

DR. HOERR: A hemoglobin of 15.5 gm. does not mean necessarily that the patient does not need blood; I visualize a shrunken total blood system, where maybe 2 or 3 pt. is needed. I want to make one additional comment, about something which has helped my thinking about the disease. A couple of times we have seen fat necrosis in the mediastinum in patients who have had attacks of acute pancreatitis, and the juice slips up there and explains some of the symptomatology, I believe.

DR. ZOLLINGER: We have observed fat necrosis over the heart. I have seen that several times, and the medical men speak of a weak electropotential as far as the electrocardiogram is concerned; I don't know what it means.

I wonder now whether we have the fluid problem solved. I have reached the conclusion that a patient with severe pancreatitis is grave-

ly ill, and that more fluid replacement is required than we tend to give to the majority of sick people. The stomach needs to be emptied, for two reasons: (1) to aspirate acid, because acid makes secretin and you are trying to keep the pancreas at rest; PRO-BANTHĪNE® or atropine is given to depress acid secretion further; (2) because of the loss of fluid into the retroperitoneal tissues and the peritoneal cavity and the loss that takes place with marked abdominal distention combined with a certain amount of hemolysis of the red blood cells, and the loss of calcium. There are some specific replacements to think about. One has to replace these losses as long as the pulse is fast and as long as the small bowel is distended. Standard fluid therapy is inadequate. Dr. Holden said that on the first day he would give calcium gluconate. I suppose he would continue this along with blood plasma or dextran as well as the usual electrolytes. Experimental and clinical evidence tends to show that this therapy is necessary for five to seven days, since it takes the pancreas several days to recover.

What are the causes of death in acute pancreatitis, Dr. Holden?

DR. HOLDEN: The principal cause of death in pancreatitis is the tremendous loss of fluids, protein and electrolytes from the blood, resulting in hypotension or shock. This is what we must combat most vigorously.

### *Steroid Therapy*

DR. ZOLLINGER: Dr. Hoerr, you mentioned steroids. Would you give steroids to a patient with pancreatitis?

DR. HOERR: Yes.

DR ZOLLINGER: To every patient who has pancreatitis?

DR. HOERR: No. The patient with severe pancreatitis. I think we would give a form of cortisone which would equate out to 200 or 300 mg. of cortisone; I don't know what modern equivalent we are using at the moment, but that is what it would amount to.

DR. ZOLLINGER: Would you give steroids, Dr. Ellison?

DR. ELLISON: I would give cortisone only if I were faced with a dying patient in a shocklike state who had not responded to the measures already discussed. Under these circumstances I would give 100 mg. of hydrocortisone intravenously.

DR. ZOLLINGER: If cortisone is good when the patient is dying, why isn't it good when dying is a possibility?

DR. ELLISON: I have not finished my story. I would give 100 mg. of hydrocortisone intravenously. If the patient is in need of cortisone, his blood pressure will rise.

DR. ZOLLINGER: How do you tell when a man is in need of cortisone?

DR. ELLISON: This is the only way I know.

DR. ZOLLINGER: He has no arthritis.

DR. ELLISON: This is the only method I know to determine this need. A patient in shock who has not responded should receive 100 mg. of hydrocortisone intravenously in a very few minutes, in 10 cc. of solution. If the blood pressure improves, he was in need of cortisone; I would continue giving it to him.

DR. ZOLLINGER: Have you seen the blood pressure come back after giving cortisone?

DR. ELLISON: Yes, when dealing with adrenal insufficiency.

DR. ZOLLINGER: What has been your experience with steroids, Dr. Holden?

DR. HOLDEN: We use the steroids on occasion. We would use them in a situation such as Dr. Ellison mentioned—not necessarily a dying patient, but one who is not responding to vigorous replacement therapy as rapidly and satisfactorily as we think he should.

DR. ZOLLINGER: You mean some days he knows you when you go in the room and some days he doesn't?

DR. HOLDEN: No; this is a matter of the first 12 hours.

DR. ZOLLINGER: Dr. Elliott, you have done some work on this, and you told me once the entire problem of pancreatitis survival was one of replacement of the plasma and blood that was lost, and if this was done that was all you had to worry about. What about steroid therapy?

DR. ELLIOTT: It is almost impossible to judge whether steroids really do any good in the cases in which they are administered, so we have tried to find an answer by producing

pancreatitis in a series of dogs. We have developed an acute pancreatitis which regularly kills the animals but from which we can obtain 100 per cent survival by giving adequate quantities of plasma or albumin. If we give just cortisone, 45 per cent of the animals survive. We think cortisone by itself is not as good as adequate plasma or colloid. It does not add anything when we give it in addition to colloid.

In treating patients, we know what we are doing when we give plasma or albumin; we are replacing a measured blood volume deficit. We know what we are doing when we give atropine and use gastric suction. I do not think we yet know a specific indication or need for cortisone in these patients.

DR. ZOLLINGER: Isn't it true that 48 per cent of the dogs in your experimental series recovered when you gave them cortisone—animals which should have died from not receiving enough colloid therapy?

DR. ELLIOTT: Cortisone produced 45 per cent recovery.

DR. ZOLLINGER: But when you gave the colloid in a smaller dose and the same steroid therapy there was no improvement?

DR. ELLIOTT: We still got 45 per cent survival. Cortisone did a little good to produce some survivals in these animals.

DR. HOERR: A little more than a year ago, I called you on the telephone about a patient who was very sick, and I followed your instructions to the letter; they included massive doses of cortisone. We got a good result, and so I am inclined to be a little prejudiced about this drug; I would be inclined to use it if the patient looks sick, not necessarily moribund, and in the absence of proof that it is going to do harm.

DR. ZOLLINGER: The reason it helped your patient is that you had not given enough colloid therapy and the other was enough boost to pull him through.

DR. HOERR: That is true; we have to give it to overcome our clinical shortcomings.

DR. ZOLLINGER: That is right. In other words, to sum this up, you don't expect to use steroid therapy except in very ill patients. From an experimental viewpoint the replacement of the colloids seems to be the treatment that insures survival; the animals usually die if an insufficient amount of colloids is given, but half of them live if steroid therapy is given. So you would give cortisone to sick patients but you don't know why it helps, is that it?

DR. ELLIOTT: That's right.

DR. ELLISON: Just so the physician does not forget all other measures once the magic drug is started.

DR. ZOLLINGER: That's right. If you start cortisone without enough of the other therapy the mortality rate will be doubled.

DR. ELLIOTT: In our animals, cortisone produces gastrointestinal hemorrhage.

DR. ELLISON: Certainly we have all seen perforation of peptic ulcers in these patients.

DR. ELLIOTT: Cortisone is not considered a harmless drug.

DR. ZOLLINGER: What about the feeling of well-being while all this is happening? That is worth a good deal.

DR. ELLISON: I would rather give testosterone for this effect.

DR. ZOLLINGER: Dr. Ellison, since you have moved to Milwaukee, have you seen more patients with pancreatitis?

DR. ELLISON: Before I moved, I thought I would not see pancreatitis in Milwaukee, because one of our colleagues in St. Louis had intimated that the problem was totally absent in his beer-drinking city. Unfortunately this is not true in Milwaukee. Perhaps we have a different kind of water.

DR. ZOLLINGER: Be careful what you say; you still live there. What has been your experience so far?

DR. ELLISON: Fifty-four cases have been seen during the past five years at the Veterans Hospital, and in the past three months I have seen eight patients with acute pancreatitis at the Milwaukee County Hospital.

### *Management After the Acute Attack*

DR. ZOLLINGER: Dr. Hoerr, the patient is over the attack of pancreatitis but he has gallbladder disease. What will you do about it?

DR. HOERR: Take out the gallbladder.

DR. ZOLLINGER: How soon?

DR. HOERR: The patient has recovered from

an attack of acute pancreatitis, is that right? I would like to wait a couple of months, hoping he would not have another attack and would not drink alcohol.

DR. ZOLLINGER: You are going to operate and remove the gallbladder. Are you going to pay special attention to the common bile duct?

DR. HOERR: I always give special attention to the common bile duct. One should always make cholangiograms in the operating room to determine whether or not common bile duct stones are present and to evaluate the situation at the sphincter.

DR. ZOLLINGER: Let us suppose the situation is very clubby with a big pancreatic duct coming right into it? What would you do?

DR. HOERR: In the absence of evidence of obstruction at the sphincter I would not do anything further. About 15 per cent of patients have a communication between the pancreatic duct and the common bile duct and never have evidence of pancreatitis.

DR. ZOLLINGER: What about the patient whose cholecystogram is normal after a severe attack of acute pancreatitis?

DR. ELLISON: If it was the primary attack and the gallbladder was normal, I would do nothing.

DR. ZOLLINGER: Do you agree, Dr. Hoerr?

DR. HOERR: Yes.

DR. ZOLLINGER: Dr. Elliott?

DR. ELLIOTT: Yes.

DR. ZOLLINGER: I thought the gallbladder was a reservoir for the incubation of mixtures of pancreatic juice and bile and should be removed to keep this from precipitating another attack. What about the diet, Dr. Elliott?

DR. ELLIOTT: After recovery, I think it is important to obtain a cholecystogram, and if it shows a normally functioning gallbladder one must also look for other signs of trouble in the pancreas, such as calcification, cysts, and so on. If there are no such findings, the patient should be treated by medical means.

DR. ZOLLINGER: What is "medical means" in the treatment of pancreatitis?

DR. ELLIOTT: The principal goal is to decrease the stimulation to the pancreas, and one can do this by using a bland diet to avoid peaks of hyperacidity.

DR. ZOLLINGER: Do you really believe a bland diet is helpful—that it will avoid these peaks of hypersecretion and avoid an attack of pancreatitis?

DR. ELLIOTT: We know that a person who has had one attack of pancreatitis has two chances out of three of having another one. We hope and believe we can prevent another episode by keeping him away from dietary indiscretions. This means avoiding alcohol and those things which stimulate gastric acid most. In addition we do use an oral atropinelike drug such as Pro-Banthine.

DR. ZOLLINGER: What about coffee, tea and cola drinks? These are acid-producing beverages and probably are more harmful to the majority of patients than alcohol. You would be surprised by the number of patients who drink 12 or 15 cups of coffee a day. Medical people use caffeine to bring out free hydrochloric acid as a test, and in any case of ulcer or pancreatitis in which you are trying to control the acid factor, if you permit the patient to drink coffee, tea or cola it will cause trouble.

### *Chronic Pancreatitis*

Dr. Holden, what about chronic pancreatitis? Is that being overplayed?

DR. HOLDEN: I believe there is plenty of evidence that pancreatitis may be a relapsing disease. I do not think there are many people who have continuous symptoms as a result of chronic inflammatory process—

DR. ZOLLINGER: When do you make a diagnosis of chronic pancreatitis?

DR. HOLDEN: After two acute attacks.

DR. ZOLLINGER: You would not include common duct stone, would you?

DR. HOLDEN: Not necessarily.

DR. HOERR: I think it is important that we differentiate these acute attacks from chronic pancreatitis.

DR. ZOLLINGER: How do you do it?

DR. HOERR: I think it is a clinical distinction. Some patients have repeated attacks of acute pancreatitis, and to me that is a different problem and possibly a different disease—or at least a different phase of the disease—from that of the patient who has daily symptoms and becomes addicted to narcotics. It is

important to make this distinction because I think good results can be obtained with cholecystectomy for stone in patients who have these recurrent attacks; good results from simple cholecystectomy are much less likely in patients who have daily symptoms.

DR. ZOLLINGER: Let us say the gallstones have been removed and there is no biliary tract pathology. How many of these cases do you see?

DR. HOLDEN: I think that is common.

DR. ZOLLINGER: What is the basis for diagnosis, then, calcification in the pancreas or cyst formation?

DR. HOLDEN: Sometimes the diagnosis is made by duodenal intubation and finding a deficient enzyme content.

DR. ZOLLINGER: What do you do? I have not used this test.

DR. HOLDEN: We use this test on occasion. We put a tube down and do a secretin test.

DR. ZOLLINGER: Isn't a secretin test a rather strenuous procedure, long to be remembered and feared?

DR. HOLDEN: I don't think it is that bad.

DR. ZOLLINGER: How many of you use it?

DR. ELLISON: I have. I never will again.

DR. ZOLLINGER: Dr. Ellison, have you any thoughts on chronic pancreatitis? The gallbladder has been removed, and all biliary tract disease has been removed.

DR. ELLISON: If the patient had gallstones initially and if all gallstone pathology is controlled, including common duct stones, I believe chances of chronic relapsing pancreatitis are very slight.

DR. ZOLLINGER: If there is calcification throughout the pancreas and the patient drinks all the time?

DR. ELLISON: In that instance the culprit is alcohol. Incidentally, I do not believe a patient has stopped drinking unless his mother, his wife, his minister and his bartender all tell me the patient is on the wagon.

DR. ZOLLINGER: I want to ask each panel member what he would do if he encountered a patient who was a derelict with pancreatitis and with calcification and whose biliary tract had been taken care of. Dr. Ellison?

DR. ELLISON: This patient must be operated on to see whether the disease process has resulted in ductal pathology, with the added factor of obstruction secondary to the chronic recurring attacks.

DR. ZOLLINGER: You would attack the papilla of Vater first?

DR. ELLISON: At operation we must determine the site of obstruction.

DR. ZOLLINGER: Do you have much hope of doing much good?

DR. ELLISON: No, because the initial cause usually is still active.

DR. ZOLLINGER: Dr. Elliott, what would you do in this case?

DR. ELLIOTT: The one additional factor you can do something about is the pancreatic duct. There is no question that ductal occlusion will precipitate recurring attacks. I agree with Dr. Ellison that one should operate and determine the site of obstruction. This may be at the sphincter. It is more likely to be inside the pancreas itself. If the pancreas is calcified, one can be quite certain that ductal obstruction is present.

DR. ZOLLINGER: If there is calcification in the pancreas, there is ductal obstruction, and the only way to correct it is with some type of surgical approach. Do you agree, Dr. Hoerr?

DR. HOERR: I agree that in some cases there will be ductal obstruction, but in some others I think it is a diffuse disease without demonstrable dilatation of the duct. The latter cases are difficult to treat. For the patient you have described, if there is ductal obstruction demonstrable we would resect the tail of the pancreas, and we have been turning the cut end of the proximal pancreas into the stomach. If it is diffuse disease, probably all one can do is resect as much of the pancreas as possible without having to subject the patient to total pancreatectomy.

DR. ZOLLINGER: Dr. Holden, what would you do?

DR. HOLDEN: I would approach this case in the same way. I would make a sincere effort to find out where the obstruction is, if I could, and then try to correct that obstruction. If it is at the sphincter, sometimes one can do a considerable amount of good. If it is in the ducts themselves, a retrograde pancreatico-

jejunostomy sometimes helps. All these things are fairly desperate measures.

DR. ZOLLINGER: Do you think there is a 50-50 chance of helping the patient with chronic pancreatitis and calcifications?

DR. HOLDEN: Not by any of these means. If there is calcification, the only procedure I have seen which helps these patients is a bilateral splanchnicectomy.

DR. HOERR: I do not think splanchnicectomy produces any permanently good effect, and I am certain that sphincterotomy is not the answer in every case.

DR. ZOLLINGER: Do you like sphincterotomy, Dr. Holden?

DR. HOLDEN: I do, when I can demonstrate either functional or organic obstruction at the sphincter.

DR. ZOLLINGER: Have you ever demonstrated it?

DR. HOLDEN: Yes.

DR. ZOLLINGER: It is odd in the history of medicine and surgery to destroy a sphincter. I never could understand it. You do it rarely?

DR. HOLDEN: Rarely, yes.

DR. ZOLLINGER: Dr. Hoerr, do you destroy it at all?

DR. HOERR: Yes, occasionally, but it is not the cure-all for this disease.

DR. ELLIOTT: Cutting the sphincter is just the first part of the job of clearing the pancreatic duct. One must make sure the duct is open all the way through the gland.

DR. ZOLLINGER: What if you split the duct all the way up, as Dr. Puestow and some others have done, and pick out the stones? Does that have merit?

DR. ELLIOTT: It has been reported in a few cases. We have done it only once so far, but with good success in opening the duct and in relieving the patient's symptoms.

DR. ELLISON: The general principles of management of chronic recurrent pancreatitis should include preservation of as much pancreatic tissue as possible while taking steps to relieve the obstruction. The pancreas must be preserved to prevent the patient from becoming a nutritional derelict.

### *Summary*

DR. ZOLLINGER: Pancreatitis is a common disease which requires energetic treatment. Symptoms often are bizarre and may defy accurate diagnosis. Determination of the serum amylase level is a valuable diagnostic test; simplified methods have been devised, and physicians who do not have serum amylase determinations available to them probably should make an issue of obtaining them. We recommend peritoneal paracentesis as a valuable diagnostic aid in puzzling cases of acute abdominal pain. The amylase levels of the peritoneal fluid remain elevated many days longer than the amylase levels of the blood serum. We recommend more enthusiasm in the use of plasma, whole blood and other replacement therapy in the treatment of acute pancreatitis. Standard fluid therapy is inadequate. We also recommend more energy in keeping the pancreas at rest during medical treatment by controlling the acid factor. From an experimental viewpoint the replacement of colloids seems to be the treatment that insures survival in pancreatitis; steroid therapy alone produced a 45 per cent survival rate in dogs, but the recovery rate was 100 per cent when adequate quantities of plasma or albumin were given. Do not always lay the blame for pancreatitis to alcoholism and gallstones; other things which people eat and drink cause trouble as well. Chronic pancreatitis requires attempts to establish free drainage of the pancreas by surgical means. There are different surgical approaches to this problem, but if a patient has had two or three or four attacks of pancreatitis and if gallbladder disease and biliary tract disease have been obliterated, then surgical consultation is in order and a proper approach should be made, without too much in the form of promise to the patient.

# Streptokinase Buccally in the Treatment of Infection and Edema

JOSEPH M. MILLER AND MILTON GINSBERG

*Surgical Service, Veterans Administration Hospital, Fort Howard, Maryland*

STREPTOKINASE should be used to reverse inflammation and edema and to inhibit the formation of edema following operation.

**Dosage**

Dosage is from 10,000 to 20,000 units every 12 hours for three days to 15 weeks.

**Observations**

- When the streptokinase was effective, changes in inflammation and edema were observed within 24 hours.
- Aggravation of infection did not occur.
- Healing of wounds was not delayed.
- A rise in temperature attributable to treatment with streptokinase was not seen.
- Pain or tenderness in the mouth and sore throat were not observed.
- Chills, cyanosis and allergic responses were not present.
- Changes in the peripheral blood picture were not seen.
- Significant alterations of the prothrombin time were not observed.
- Untoward hemorrhage was not present.

**Precautions**

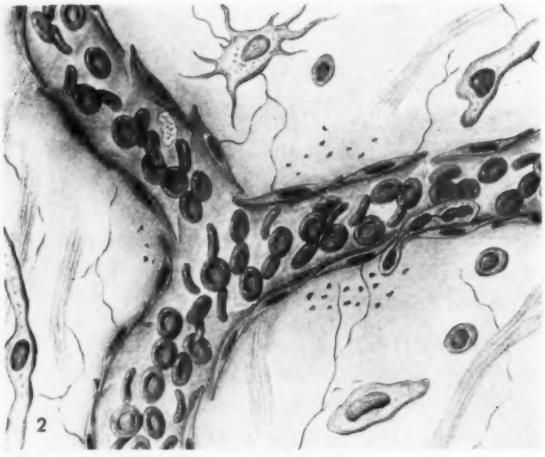
Adequate circulation to the involved area must be present.

An antibacterial drug must be given with buccally administered streptokinase when infection is present or suspected.

Streptokinase should not be given to patients with defects in the clotting mechanism.

Streptokinase should not be given to patients with a history of one of the collagen diseases or during an attack of one of these diseases.

Adapted from the exhibit presented at the 1958 clinical session of the American Medical Association, Minneapolis, Minnesota.



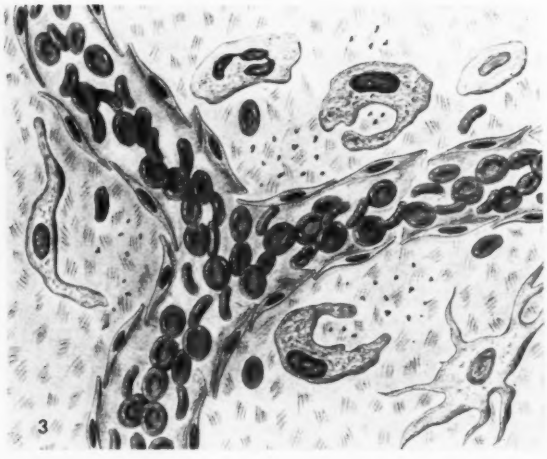

## Mechanism of Action of Streptokinase

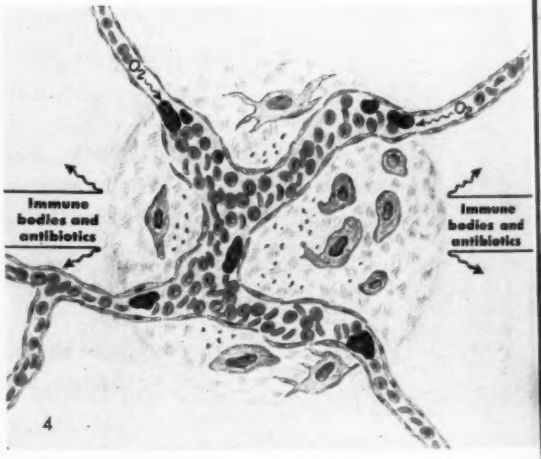
1. Normal tissues.

2. The bacteria in tissues start the inflammatory reaction and the capillaries become congested and dilated. The walls of the capillaries are more permeable. The phagocytes are beginning to be mobilized.

3. Macromolecular proteins are deposited in the tissues, perhaps due to the failure of a fundamental proteolytic process. This lack of proteolysis may be secondary to the presence of a chemical inhibitor or a change in pH of the environment. The content of water in the area increases and swelling becomes apparent.

4. The capillaries are smaller, and thrombi are forming with resultant hypoxia or even anoxia. A wall of protein is being created about the site in an effort to isolate the infection. The wall prevents the ingress of humoral forces and administered antibacterial drugs.

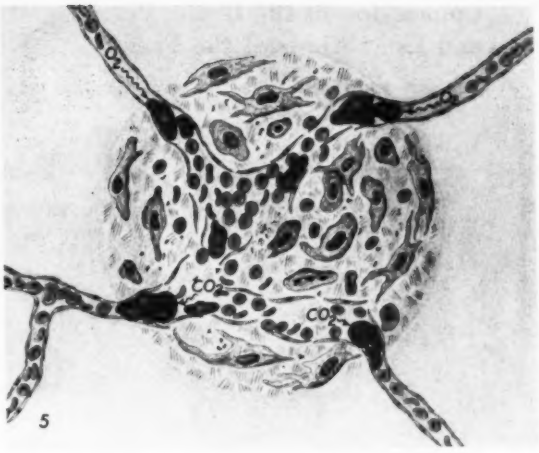


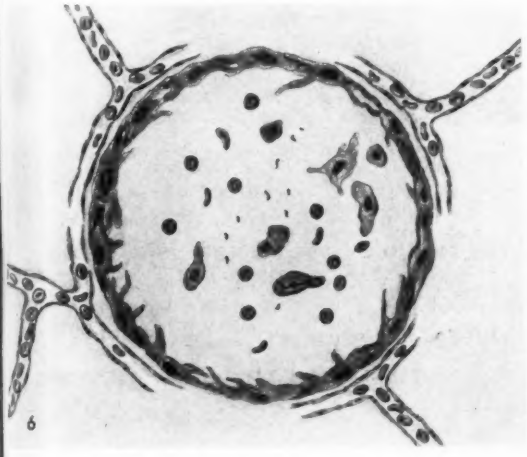
5. The host defenses successfully isolate the infection but thereby produce death of the sequestrated tissue.

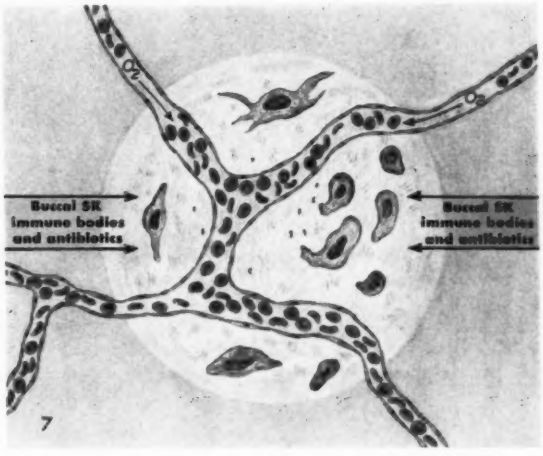
6. The end stage is death of the tissue. The humoral forces and the administered antibacterial drugs are worthless in the treatment of an abscess, although they may help the surrounding inflamed tissue.

7. The theory of the reversal of a cellulitis by the humoral forces and the administered antibacterial drugs.



5


6

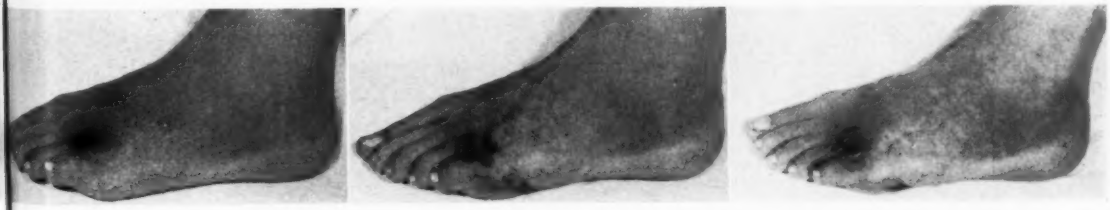


7

## Abscess and Cellulitis of the Left Foot

Ten thousand units of streptokinase every 12 hours from November 2, 1956 through November 5, 1956.

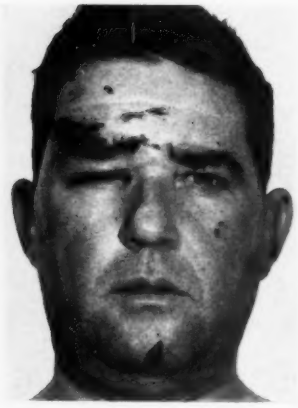
November 2, 1956 November 3, 1956 November 6, 1956



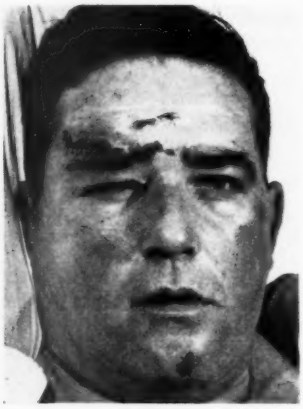
## Concussion of the Brain, Fracture of the Occipital Bone, and Lacerations of the Face

Ten thousand units of streptokinase every 12 hours from November 2, 1956 through November 7, 1956.

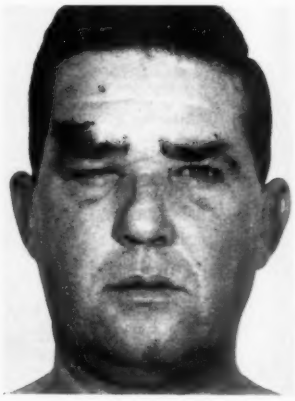
November 2, 1956



November 3, 1956



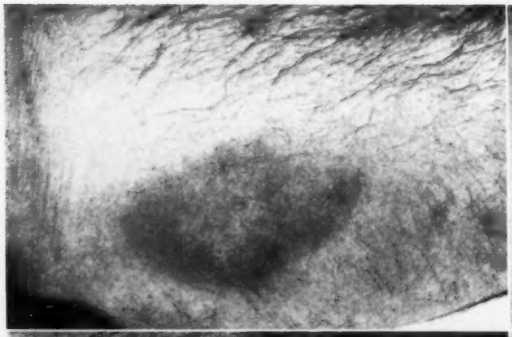
November 6, 1956



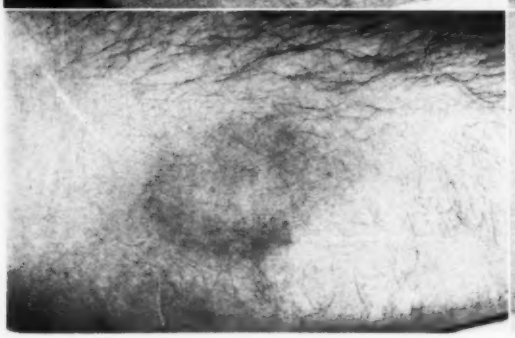
## Intradermal Skin Test

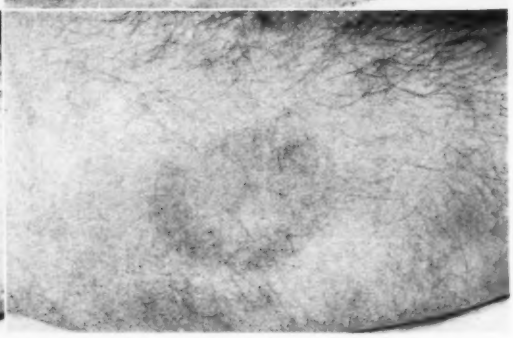
Ten thousand units of streptokinase every 12 hours from November 28, 1956 through December 1, 1956.

November 28, 1956



November 29, 1956





November 30, 1956

December 1, 1956

## Thrombophlebitis of the Right Lower Extremity

Ten thousand units of streptokinase every 12 hours from November 27, 1956 through November 29, 1956.

November 27, 1956

November 28, 1956

November 29, 1956

November 30, 1956

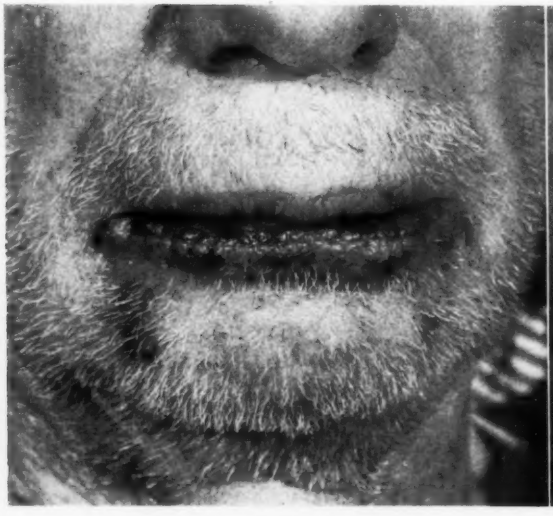
## Excision of Hyperkeratosis of the Lower Lip

Ten thousand units of streptokinase every 12 hours from January 8, 1957 through January 12, 1957.

January 8, 1957

January 10, 1957

January 15, 1957



January 23, 1957

From Miller, J. M., Godfrey, G. C., Ginsberg, M. and Papastrat, C. J. Clinical experience with streptokinase administered buccally; treatment of infection and edema. J.A.M.A. 166:479-481 (February 1) 1958.

## Carbuncle of the Right Lower Extremity

Twenty thousand units of streptokinase every 12 hours from January 15, 1957 through February 28, 1957.

January 30, 1957

February 3, 1957

February 5, 1957

February 13, 1957

February 19, 1957

**First, Second and Third Degree Burns of the Face, Neck, Thorax, Abdomen, Left Upper Extremity and Right Hand**

January 26, 1958 January 28, 1958

Twenty thousand units of streptokinase every 12 hours from January 26, 1958 through May 9, 1958.

February 3, 1958 February 8, 1958 May 29, 1958

## Hyphema of the Left Eye and Fracture of the Left Zygomatic Bone

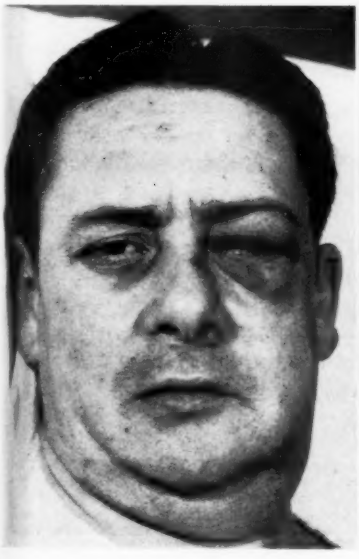
Twenty thousand units of streptokinase every 12 hours from February 4, 1958 through February 13, 1958.

February 4, 1958



February 5, 1958

February 6, 1958



February 7, 1958

February 10, 1958

## The Buccal Administration of Streptokinase

The tablet should be permitted to dissolve in the mouth within five minutes, and the patient should be advised not to swallow or expectorate during this period of time.

## Conclusions

1. Streptokinase given buccally produces a modification of the inflammatory reaction and resorption of edema.

2. Treatment with streptokinase given buccally must be accompanied by the administration of an antibacterial drug when infection is present or suspected.

3. The use of streptokinase given buccally is not a substitute for sound surgical treatment.

# A Method for Planning Diets to Lower Serum Cholesterol

PATRICIA A. STEFANIK* AND MARTHA F. TRULSON†

*Harvard University School of Public Health, Boston*

THE dietary management of hypercholesteremia has received impetus from strong evidence of a direct association between diet and levels of serum cholesterol in man and from the postulated relationship of serum cholesterol to the development of ischemic heart disease. It is generally agreed that (1) saturated fats of either animal or vegetable origin raise total serum cholesterol, (2) some highly unsaturated (polyunsaturated) fats of either marine or vegetable origin tend to lower serum cholesterol, and (3) fats with an intermediate degree of saturation exert little influence. As new knowledge in this field becomes available, clinicians continually seek methods by which it may be practically applied to diets which, over a long period, may delay the onset or progress of atherosclerosis. Because of some of the recently recognized effects of different dietary fats on serum lipids, attempts have been made to modify food intake by adjusting the type of fat to proportions different from those found in the typical American diet.

*Instructor in Nutrition; †Department of Nutrition, Harvard University School of Public Health, Boston, Massachusetts.

This study was supported in part by grants from the John A. Hartford Memorial Fund, the Lasker Foundation, and the Nutrition Foundation, Inc., New York, New York, and the Fund for Research and Teaching, Department of Nutrition, Harvard University School of Public Health, Boston, Massachusetts.

PATRICIA A. STEFANIK

MARTHA F. TRULSON

For many years, hypercholesteremia and ischemic heart disease were managed chiefly by a rigid limitation of the total dietary intake of fat in proportion to total calories. Two long-term trials[1,2] which assessed the therapeutic effect of total fat restriction indicated a longer survival rate in patients who followed this regimen than in those who did not. Patients with hypercholesteremia who were fed a rice diet for both short periods and periods of up to 11 years exhibited sizable reductions of total serum cholesterol concentration.[3] The opposite extreme, a high fat diet, usually fed in formula form to standardize diets with highly unsaturated fats, also has proved successful in lowering serum cholesterol; however, be-

TABLE 1

PER CENT OF WEIGHT OF MIXED FATTY ACIDS IN EGG YOLK ACCORDING TO DIET FED TO HENS*

| ACIDS | CONTROL MASH | MASH AND LINSEED OIL | MASH AND HEMP OIL | HEMPSEED ALONE |
|---|---|---|---|---|
| Saturated acids | 31.4 | 23.9 | 24.3 | 21.4 |
| Oleic acid | 47.4 | 37.9 | 23.5 | 25.3 |
| Linoleic acid | 19.0 | 17.4 | 49.6 | 44.1 |
| Linolenic acid | 2.2 | 20.8 | 2.6 | 9.2 |

* Adapted from Hilditch, T. P.[12]

TABLE 2

TYPICAL ANALYSES OF FATTY ACIDS IN SOME FATS OF ANIMAL AND PLANT ORIGIN*

| ORIGIN | SATURATED (Total) | UNSATURATED | | |
|---|---|---|---|---|
| | | *Oleic* | *Linoleic* | *Others* |
| Animal Fats | | | | |
| Lard | 43.5 | 47.8 | 3.1 | 5.6† |
| Chicken | 32.9 | 39.4 | 21.8 | 5.9† |
| Butterfat | 60.0 | 29.5 | 3.6 | 7.2† |
| Beef fat | 53.6 | 41.1 | 1.8 | 3.5† |
| Vegetable Oils | | | | |
| Corn | 10.7 | 30.1 | 56.3 | 2.9 |
| Peanut | 17.1 | 61.1 | 21.8 | |
| Cottonseed | 27.2 | 22.9 | 47.8 | 2.1 |
| Soybean | 13.4 | 28.9 | 50.7 | 7.0‡ |
| Olive | 13.9 | 77.5 | 8.6 | |
| Coconut | 91.2 | 7.5 | TR | 1.3‡ |

*From The Role of Dietary Fat in Human Health. National Research Council Publication No. 575, Washington, D.C., 1958.

†Mostly hexadecenoic acid; 0.2 to 0.4 per cent arachidonic acid.

‡Mostly linolenic acid.

cause this type of diet is poorly applied to everyday living, it has been unpopular outside the hospital.

Comparable results in reducing serum cholesterol have been shown in short-term therapeutic trials of diets in which some foods high in saturated fatty acids are removed and the amount of foods high in polyunsaturated fatty acids is sharply increased. The combination of these two modifications produces a practical dietary regimen that is acceptable to most patients. A diet similar to either the vegetarian or the low animal fat regimen with added vegetable oil has been used with equal success.[4-7] Although the degree of response varies in different persons, the cholesterol-lowering effect apparently is similar in normal persons, in patients with ischemic heart disease (with or without hypercholesteremia), and in young, middle-aged and elderly men and women. Reduction of serum cholesterol reaches a maximum in two to three weeks, the total decrease being 20 to 30 per cent. This decrement is maintained until the patient resumes his ordinary diet.

As a result of clinical experiments such as these, theories concerning diets for patients with hypercholesteremia have ranged from the total restriction of fat to allowances of high fat and completely unsaturated fatty acid; the present theory is an allowance between these two extremes. Here, the chief objective is the selection of foods to obtain a higher ratio of polyunsaturated fatty acids to saturated fatty acids, with a moderate proportion of total fat in relation to total calories.

TABLE 3

OUTLINE OF MODIFIED FATTY ACID DIET PROVIDING 80 GM. PROTEIN, 90 GM. FAT, AND 2000 CALORIES[15]

| FOOD GROUP | AMOUNT | CALORIES | PROTEIN (GRAMS) | FAT (GRAMS) | FATTY ACIDS (GRAMS) | |
|---|---|---|---|---|---|---|
| | | | | | *Saturated* | *Polyunsaturated** |
| Basic diet plan | | | | | | |
| Meat, fish and poultry† | 7 oz. | 367 | 40 | 21 | 8.52 | 2.50 |
| Skim milk | 2 cups | 174 | 17 | 0.5 | 0.21 | 0.03 |
| Egg | 1 | 77 | 6 | 5.5 | 1.64 | 1.48 |
| Fruits and vegetables | 5 average servings | 240 | 3 | 1 | 0.10 | 0.60 |
| Bread or cereals, or both | 3 average servings | 227 | 6.5 | 1.5 | 0.34 | 0.75 |
| Potato and substitutes | 2 average servings | 220 | 7 | 1 | 0.10 | 0.60 |
| Sugar and sweets | 3 tablespoons | 165 | | | | |
| TOTAL | | 1,470 | 79.5 | 30.5 | 10.91 | 5.96 |
| Fat allowance | | | | | | |
| Vegetable oil | 2 oz. (4 tablespoons) | 530 | | 59.5 | ‡ | ‡ |
| TOTAL | | 2000 | 79.5 | 90 | | |

*Chiefly linoleic acid.

†Daily averages based on a seven day food intake. The figures for meat, fish and poultry are taken from raw weights for 420 gm. chicken, 315 gm. low fat fish, 105 gm. liver, and 210 gm. each of lean beef, veal and lamb per week.

‡Variable, depending on oil used. For example, 2 oz. (4 tablespoons) corn oil provides 6.0 gm. saturated and 33.6 gm. polyunsaturated fatty acids (31.8 gm. linoleic acid). Daily total of saturated fatty acids is 16.91 gm. (8 per cent of calories) and total polyunsaturated fatty acids 39.56 gm. (18 per cent of calories). Table 4 gives other oils with high ratios of linoleic acid.

Two factors limit the selection of a regimen of modified fatty acid: (1) Analyses of fatty acid in most foods are so limited that accurate diet calculations are practically impossible, and, at best, only estimations can be made, and (2) the optimal quantities or proportions of saturated and polyunsaturated fatty acids are uncertain.

Few reports of the amounts of fatty acids in the normal American diet have been made. However, from a survey of retail foods purchased in 1955, the United States Department of Agriculture[8] estimated that about 18 per cent of daily total calories are furnished by saturated fats, and 4.5 per cent are derived from linoleic acid. Other investigators[9-11] determined approximately the same estimations for saturated and polyunsaturated fatty acids (mostly linoleic acid) from studies of food intake.

It is difficult to calculate dietary fatty acids, since the composition of a single food may vary greatly. For example, the variety of a plant, the processing of the seed and oil, and the breed of animal and the diet which it is fed influence the product. The marketed product may be altered by processing, cooking and/or storage. A rather striking illustration of the variance in the fatty acid content of a food is that found in egg yolk.[12] Depending on the diet fed to the hen, egg fat may have as little as 15 per cent linoleic acid, or it may contain as much as 50 per cent (table 1). The development of more highly refined technics for analyzing the characteristics of fats and oils is necessary before extensive data will be available on the fatty acids of foods marketed in this country. The United States Department of Agriculture is now compiling current information on fatty acids in animal and plant products from sources in this country and in others.[13] Typical analyses of the fatty acids in some fats of animal and plant origin are shown in table 2.

With the exception of marine animals and their products (many of which contain poly-

unsaturated fatty acids of chain lengths longer than linoleic acid), a high content of the polyunsaturated fat linoleic acid is commonly found in those fats which lower serum cholesterol in man.[14] Hypercholesteremia has been reduced by intake of diets in which linoleic acid represents between 15 and 20 per cent of the total calories. In comparison with the normal diets to which people in this country are accustomed, this represents approximately a threefold increase in the percentage of equivalent total fat calories derived from polyunsaturated fatty acids. Most people can easily adhere to diets with this increased proportion of calories from linoleic acid. Because results are generally rewarding, diets modified to this degree gradually are being used more.

### *Dietary Procedure*

The following discussion outlines a plan for altering the percentage of calories from or the ratio between fatty acids in the diet. Based in part on the types of diets used in the clinical trials mentioned previously, the daily food allowance is designed so that total calories of fat are maintained at approximately 40 per cent and calories of linoleic acid at 15 to 20 per cent of the total calories.

The basic diet plan in table 3 indicates the types and amounts of foods which will provide 30 gm. fat, 80 gm. protein, and 1500 calories daily.[15] The estimated content of fatty acid is 6 gm. polyunsaturated (chiefly in the form of linoleic acid) and 11 gm. saturated, or a ratio of approximately 1:2. To this basic plan is added a daily allowance of vegetable oil which contains a high ratio of linoleic acid. Two ounces of oil will change the total fat content from 30 to 90 gm. and the total calories from 1500 to 2000 and will reverse the ratio of linoleic acid in relation to saturated fatty acids. For example, the fatty acids provided in 2 oz. corn oil produce a total estimated daily fat intake supplying 39.6 gm. polyunsaturated and 16.9 gm. saturated fatty acids. This provides 18 per cent of the total calories from polyunsaturated fat and 8 per cent from saturated fat, or a 2.25:1 ratio.

The ratio of linoleic acids to saturated fatty acids serves as a guide in choosing foods containing fat. Ratios of the component linoleic and saturated fatty acids for some common foods are shown in table 4. The figure representing the composite fatty acid in meat, fish and poultry in the basic diet plan is derived from a combination of foods with a very low linoleic acid ratio—beef, veal, lamb and liver—and foods with a medium linoleic acid ratio—poultry and fish. The total weekly allowance of this food group on the basis of raw weight of edible portion is approximately 1½ lb. beef, lamb, veal and liver and 1½ lb. chicken, turkey and low fat fish.

The following foods should be excluded from a diet containing modified fatty acids:

TABLE 4

RATIO OF LINOLEIC ACID TO SATURATED FATTY ACID CONTENT OF FOOD FATS*

| FATS | RATIO OF LINOLEIC ACID TO SATURATED FATTY ACID |
|---|---|
| *High* | |
| Safflower oil† | 9.0 |
| English walnuts | 8.9 |
| Sunflower oil | 5.3 |
| Corn oil | 5.3 |
| Soybean oil | 3.5 |
| Cottonseed oil | 2.0 |
| *Medium* | |
| Salmon fat‡ | 1.7 |
| Peanut oil | 1.6 |
| Nuts§ | 1.5 |
| Tuna fat‡ | 0.7 |
| Turkey fat‡ | 0.7 |
| Olive oil | 0.6 |
| Chicken fat‡ | 0.6 |
| Egg fat‡ | 0.2 |
| *Low* | |
| Margarine | 0.3 |
| Vegetable shortening | 0.3 |
| Pork fat | 0.2 |
| Butter | 0.1 |
| Milk fat | 0.1 |
| Beef fat | 0.1 |
| Lamb fat | 0.1 |
| Coconut oil | 0.1 |

*Adapted from report.[15]

†Not marketed for household use.

‡Contains substantial amounts of arachidonic acid or other higher-chain unsaturated fatty acids or both.

§Composite including almonds, brazil nuts, cashew nuts, filberts, peanuts, pecans and pistachio nuts.

TABLE 5

SAMPLE MENUS FOR A MODIFIED FATTY ACID DIET

| | | |
|---|---|---|
| BREAKFAST | | |
| ½ cup orange juice | ½ cup grapefruit juice | 1 orange |
| 1 egg, scrambled with ½ tablespoon oil | 2 slices French toast, made with 1 egg, skim milk and 1½ tablespoons oil | ¾ cup flaked cereal |
| 1 slice toast | Syrup | 1 glass skim milk |
| Jelly | Beverage, if desired | Sugar |
| Sugar | | Beverage, if desired |
| Beverage, if desired | | |
| LUNCH | | |
| 3 oz. (raw weight) lean roast beef | 4 oz. (raw weight) veal cutlet, breaded and fried with 1½ tablespoons oil | Sandwich containing 1 egg, 2 slices bread, 1 rounded tablespoon mayonnaise* |
| Potato, browned with 1 tablespoon oil | Large potato, plain | Fresh apple |
| Baked squash, plain | ½ cup spinach | 2 medium-sized sugar cookies containing 1 teaspoon oil |
| Vegetable salad with 1 tablespoon oil | ½ cup carrots | 1 glass skim milk |
| 1 slice bread | ¼ medium-sized cantaloupe | Beverage, if desired |
| 1 glass skim milk | 1 glass skim milk | |
| Beverage, if desired | Jelly | |
| | Beverage, if desired | |
| DINNER | | |
| 4 oz. (raw weight) chicken breast, broiled with 1 tablespoon oil | 3 oz. water-packed tuna salad, made with 1 rounded tablespoon mayonnaise, lettuce and celery | 6 oz. tomato juice with 1 tablespoon oil |
| Spanish rice, baked with ½ tablespoon oil | 4 Saltines | 7 oz. (raw weight) haddock, baked with 1 tablespoon oil |
| ½ cup green peas, plain | Lime ice | Large baked potato |
| 1 slice bread | 1 glass skim milk | ½ cup corn |
| Jelly | Beverage, if desired | ½ cup green beans |
| 1 glass skim milk | | 1 piece strawberry chiffon pie containing 2 teaspoons oil |
| JELL-O® with sliced peaches | | Beverage, if desired |
| Beverage, if desired | | |

*1 rounded tablespoon mayonnaise is equivalent to 1 tablespoon oil.

whole milk; bread made with large amounts of hydrogenated shortening; desserts made with chocolate, cream, hydrogenated shortening, margarine, butter or whole milk; butter, cream, margarine, hydrogenated shortening; fat meat or fowl; fish or poultry prepared with hydrogenated shortening, margarine or butter; and all cheese except dry cottage cheese and cheese made with skim milk; potato chips and potatoes prepared with hydrogenated shortening; soups containing cream, animal fat or whole milk; candy made with chocolate, cream, whole milk or butter; gravy made from animal fat drippings; hydrogenated peanut butter; and white sauce made with butter or hydrogenated vegetable products.

The greatest advantage of the modified fatty acid diet is that it permits meal patterns consistent with food practices in most localities. The variety of foods allowed, the inclusion of a substantial amount of calories from fat for more palatability, and the wider choice of permissible methods for food preparation promote its continuous use for a long period.

The sample menus given in table 5 are based on the diet outline in table 3 and are given as a guide for planning daily menus.

Cooking methods need not be limited as long as the allowance of oil is not exceeded. Salad dressings made with oil may be used as part of the daily allowance. Baked goods, if prepared with nonhydrogenated vegetable oil not exceeding the daily allowance, are not excluded unless there is a restriction of total calories for weight reduction. Vegetable oils rather than separated fats may be used in most basic recipes. Some cookbooks show fat substitutions or technics of low fat cookery.[16]

A special-purpose margarine, containing corn oil with an unmodified polyunsaturated fatty acid content as the main fat, has been used as a substitute for the ordinary solid fats

in modified fatty acid diets.[5,7] This preparation may be used as a part of the allowance of vegetable oil for cooking, for flavoring vegetables, or for a spread. However, if used for general household consumption, the cost of this product may be somewhat prohibitive. Another new margarine which is a hydrogenated corn oil product is also available; however, whether or not this corn oil margarine is advantageous as a replacement for other vegetable margarines or shortenings with like total unsaturation is to our knowledge still indefinite.


### *Summary*

The extent of dietary changes which are necessary to modify the proportion of calories from polyunsaturated fatty acids is based on the estimated average diet in the United States. However, it must be added that the individual variation in daily dietary intake is great; therefore, the degree of exchanges in food fats as presented in the modified fatty acid regimen cannot be assumed to be ideal for all persons with hypercholesteremia or a tendency toward elevated serum lipids.



Bulk quantities of reprints of this article are available at special rates on request to the Editorial Department, POSTGRADUATE MEDICINE, Essex Building, Minneapolis 3, Minnesota.


### REFERENCES


1. LYON, T. P., YANKLEY, A., GOFMAN, J. W. and STRISOWER, B.: Lipoproteins and diet in coronary heart disease. California Med. 84:325 (May) 1956.
2. MORRISON, L. M.: A nutritional program for prolongation of life in coronary atherosclerosis. J.A.M.A. 159:1425, 1955.
3. KEMPNER, W., PESCHEL, R. L. and SCHLAYER, C.: Effect of rice diet on diabetes mellitus associated with vascular disease. Postgrad. Med. 24:359 (October) 1958.
4. BROWN, H. B. and PAGE, I. H.: Lowering blood lipid levels by changing food patterns. J.A.M.A. 168:15, 1958.
5. TERMAN, L. A.: Dietary management of hypercholesterolemia. Geriatrics 14:111, 1959.
6. RHOADS, D. V. and BARKER, N. V.: Effect of reduction of dietary fat and additional ingestion of corn oil on hypercholesterolemia. Proc. Staff Meet. Mayo Clin. 34:225, 1959.
7. BOXER, P. A., LOWER, J. T., GARDIER, R. W. and RALSTON, J. D.: Effect of a practical dietary regimen on serum cholesterol level. J.A.M.A. 170:257, 1959.
8. Dietary Levels of Households in the West. Household Food Consumption Survey Report No. 10, 1955. Washington, D.C., United States Department of Agriculture (July) 1957.
9. KEYS, A., ANDERSON, J. T. and GRANDE, F.: Prediction of serum cholesterol responses of man to changes in fats in the diet. Lancet 2:959, 1957.
10. MCCANN, M. B. and TRULSON, M. F.: Our changing diet. J. Am. Dietet. A. 33:358, 1957.
11. Department of Nutrition, Harvard University School of Public Health: Unpublished data.
12. HILDITCH, T. P.: The Chemical Constitution of Natural Fats. New York, John Wiley & Sons, Inc., 1956.
13. Fatty Acids in Food Fats. Home Economics Research Report No. 7. Washington, D.C., United States Department of Agriculture (March) 1959.
14. PORTMAN, O. W.: Dietary factors and the serum cholesterol level. Postgrad. Med. 26:386, 1959.
15. STEFANIK, P. A. and TRULSON, M. F.: Modifying the fatty acid content of the diet. J. Am. Dietet. A. 34:591, 1958.
16. KEYS, A. and KEYS, M.: Eat Well and Stay Well. New York, Doubleday & Company, Inc., 1959.

CLINICAL STUDY

# Treatment of the Premenstrual Tension Syndrome With Ethisterone and Other Agents

ROBERT S. MUTCH*

*Pennsylvania Department of Health, Harrisburg*

*A group of 149 women with the premenstrual tension syndrome were given two compounds containing ethisterone and other agents; one compound contained perphenazine. Forty-two had complete relief of symptoms, and 76 per cent were improved. Further trial of these agents is warranted.*

ROBERT S. MUTCH

THE premenstrual tension syndrome usually begins 10 to 14 days premenstrually, reaches a climax shortly before menstruation, and is resolved abruptly when menstruation begins. The syndrome is negligible in many women, but many others are victims of distressing mental and physical symptoms. The most common complaints are mild depression, anxiety, emotional lability, fatigue, insomnia, weakness, increased appetite (especially for sweets), mastodynia, abdominal bloating, nausea, vomiting, pains in the legs and lower back and abdomen, urinary frequency, weight gain, urticaria, stomatitis and exacerbation of dermatologic conditions.

The mechanism of premenstrual tension is not known precisely, although many theories have been postulated. There is increasing evidence of an estrogen-progesterone imbalance, as described by Frank,[1] Thorn and colleagues,[2] and Mazer and Israel.[3] Endometrial biopsies, vaginal smear tests, analyses of urinary hormones, and studies of daily basal temperature indicate decreasing progesterone stimulation with uninhibited utilization of estrogen during the premenstrual phase, occurring with changes in sodium metabolism and consequent sodium retention.[2,4] The significance of fluid retention in the etiology of premenstrual tension has been confirmed clinically. Administration of a diuretic agent is often sufficient

*Director of Employee Health, Pennsylvania Department of Health, Harrisburg, Pennsylvania.

to relieve symptoms.[5,6] The premenstrually elevated estrogen level suppresses production of pituitary growth hormone, which is believed to stimulate production of the hyperglycemic-glycogenolytic factor by the alpha cells of the pancreatic islets; this suppression provokes hypoglycemia.[3,4,7] The psychic effects probably are secondary to hormone inhibition and may be mediated through the hypothalamus-pituitary axis or the autonomic nervous system.

Treatment of premenstrual tension is directed toward neutralization of the unantagonized estrogen or control of its untoward effects at different levels. Thus, progesterone, testosterone, chorionic gonadotropin, roentgen therapy, vitamin B complex, salt restriction, diuretics, and antihistamines have been recommended for this condition.

### *Materials*

Two compounds containing ethisterone and other agents were made available for clinical trial.* Ethisterone Compound C contains, in each tablet, 10 mg. ethisterone (PRANONE®), 2 mg. chlorprophenpyridamine maleate (CHLOR-TRIMETON®), 25 mg. 8-bromotheophylline, 300 mg. salicylamide, and 30 mg. caffeine. Ethisterone Compound T contains the same ingredients plus 4 mg. perphenazine (TRILAFON®).

Ethisterone is a progestin and is used to supplement the corpus luteum hormone, which is relatively deficient during the premenstrual period. The active xanthine diuretic 8-bromotheophylline alleviates the water retention caused by the disturbed electrolyte balance. Chlorprophenpyridamine is included because antihistamines are thought to relieve hypersensitivity to the relatively high premenstrual levels of estrogen.[8] Caffeine is a central nervous system stimulant used widely to combat drowsiness, fatigue and depression.[9] It is thus valuable for relief of these symptoms occurring as part of the premenstrual tension syndrome. Perphenazine is an extremely potent tranquilizer and antiemetic.[10] It is particularly effective, in low doses, against anxiety, nervousness, irritability and nausea, common components of the syndrome.

*Provided through the courtesy of R. Richard McCormick, M.D., Division of Clinical Research, Schering Corporation, Bloomfield, New Jersey.

TABLE 1

TREATMENT OF THE PREMENSTRUAL TENSION SYNDROME WITH ETHISTERONE AND OTHER AGENTS; IMPROVEMENT WITH THERAPY

| RESULT | COMPOUND C* (62 PATIENTS) | COMPOUND T† (87 PATIENTS) |
|---|---|---|
| Complete relief | 16 (26%) | 26 (30%) |
| Major improvement | 16 (26%) | 18 (21%) |
| Slight improvement | 13 (21%) | 25 (28%) |
| No improvement | 17 (27%) | 18 (21%) |
| TOTAL IMPROVED | 45 (73%) | 69 (79%) |

Total improved for both groups, 114 (76%)

*Ten mg. ethisterone, 2 mg. chlorprophenpyridamine, 25 mg. 8-bromotheophylline, 300 mg. salicylamide, and 30 mg. caffeine.

†Same ingredients as are found in Compound C plus 4 mg. perphenazine.

### *Method*

A group of 261 women, office workers in an urban area, volunteered to participate in the study. All had premenstrual tension. The frequency of symptoms was as follows: nervousness or anxiety, 239 patients; personality alterations, 195; emotional lability, 167; breast tenderness, 167; increased cervical secretions, 78. Headache, bloating, nausea, vomiting, pain in the legs or lower back, cramps, weight gain, edema of the ankles, urticaria, acne and pica were all reported frequently enough to be of significance.

Of the 103 women who were given ethisterone Compound C, 62 returned for follow-up and were included in the series. Of the 158 who received ethisterone Compound T, 87 returned and were included.

In both groups the usual dosage was 1 tablet daily for six days before the expected onset of menstruation; occasionally 2 tablets daily were required. Most of the women were treated for one or two months, and a few for three months.

Results were evaluated according to the fol-

TABLE 2

SYMPTOMS REPORTED DURING THERAPY OF THE PREMENSTRUAL TENSION SYNDROME WITH ETHISTERONE AND OTHER AGENTS

| SYMPTOM | COMPOUND C (62 PATIENTS) | COMPOUND T (87 PATIENTS) |
|---|---|---|
| Dysmenorrhea | 5 | 7 |
| Early menstruation | 1 | 6 |
| Delayed menstruation | 1 | 4 |
| Headache | 2 | 2 |
| Menorrhagia | | 4 |
| Drowsiness | 1 | 2 |
| Dizziness | 1 | 1 |
| Nausea | | 2 |
| Nervousness | 2 | |
| Urinary frequency | 1 | 1 |
| Bloating | 1 | |
| Depression | | 1 |
| Breast sensitivity | | 1 |
| Acne | 1 | |
| Urticaria | | 1 |
| TOTAL | 16 (26%) | 32 (37%) |

Total for both groups, 48 (32%)

lowing criteria. Disappearance of all signs and symptoms was graded as complete relief. Marked alleviation of nearly all symptoms was considered major improvement. If only one or a few symptoms were relieved, improvement was considered slight.

### *Results*

Of the 149 women who returned for follow-up, 114 (76 per cent) evidenced at least some degree of improvement (table 1). Symptoms reported during therapy are summarized in table 2. Since these symptoms are components of the premenstrual tension syndrome, they cannot be considered side effects of the drug preparations.

### *Summary and Conclusion*

Preliminary results indicate that both ethisterone Compound C and ethisterone Compound T are effective in most cases of the premenstrual tension syndrome. Further trial with these agents is warranted. Both drugs provided good relief. The compound with perphenazine is preferred when emotional factors predominate.

REFERENCES

1. FRANK, R. T.: Hormonal causes of premenstrual tension. Arch. Neurol. & Psychiat. 26:1053-1057 (November) 1931.
2. THORN, G. W., NELSON, K. R. and THORN, D. W.: A study of the mechanism of edema associated with menstruation. Endocrinology 22:155-163 (February) 1938.
3. MAZER, C. L. and ISRAEL, S. L.: Diagnosis and Treatment of Menstrual Disorders and Sterility. Ed. 3. New York, Paul B. Hoeber, 1951.
4. MORTON, J. H.: Premenstrual tension. Am. J. Obst. & Gynec. 60:343-352 (August) 1950.
5. BICKERS, W.: Premenstrual tension; a water toxicity syndrome. Virginia M. Month. 85:613-615 (November) 1958.
6. JUNGCK, E. C., BARFIELD, W. E. and GREENBLATT, R. B.: Chlorothiazide and premenstrual tension. J.A.M.A. 169:112-114 (January 10) 1959.
7. HOGE, R. H.: Premenstrual tension. Virginia M. Month. 85:8-11 (January) 1958.
8. REBHUN, J.: Allergy to estrogens. Ann. Allergy 15: 647-657 (November-December) 1957.
9. GOODMAN, L. S. and GILMAN, A.: The Pharmacological Basis of Therapeutics. Ed. 2. New York, The Macmillan Company, 1956, p. 340.
10. PREISIG, R. and LANDMAN, M. E.: Use of perphenazine in anxiety states and hyperemesis; report of 135 cases. Am. Pract. & Digest Treat. 9:740-744 (May) 1958.

CLINICAL STUDY

# Chymotrypsin Therapy of Peptic Ulcer; Results in 78 Cases

A. A. MOZAN

*Chicago*

*Chymotrypsin was used alone or in conjunction with other medicaments in 78 cases of peptic ulcer. Concomitant use of anticholinergic drugs and tranquilizing agents enhances the healing properties of chymotrypsin by affording rest to the involved portion of the stomach and by relieving psychic stress. Results obtained lead the author to recommend use of the enzyme as a valuable adjunct in treating peptic ulcer.*

A. A. MOZAN

ENZYMES have steadily attained a position of therapeutic importance, and the scope of their therapeutic application is widening rapidly. In 1933, Tillett and Garner[1] reported that broth cultures of hemolytic streptococci obtained from patients were capable of liquefying a fibrin clot in human beings. It later was demonstrated that the liquefaction of the clot was due to the enzymes streptokinase and streptodornase. Subsequently, interest was focused on the use of other enzymes such as trypsin in an attempt to produce thrombolysis.

Further studies demonstrated that trypsin not only caused lysis of fibrin in vitro but also was capable of initiating such activity in vivo by converting profibrinolysin (plasminogen) to the active fibrinolysin (plasmin). Its ability to produce thrombolysis naturally led to its use in the treatment of intravascular thrombotic disease. By administering this enzyme intramuscularly instead of intravenously and by decreasing the dose, its use was made safer and more practical. Because of its widened application, another interesting and important effect was noted, namely, its antiphlogistic action.

At about the same time, Innerfield, Angrist, Schwarz and Ruggiero,[2] Fisher and Wilensky,[3] and Golden[4] observed that it was effective in the treatment of such diverse diseases as thrombophlebitis, phlebothrombosis, chronic stasis ulcer, and other types of inflammation. The use of streptokinase, trypsin and chymotrypsin in the treatment of such refractory and chronic diseases proved that they would reactivate a bogged-down healing process to such a degree as had rarely been observed previously. The antiphlogistic power of

these enzymes to alter chronicity in cases of thrombotic disease was most astonishing.

Several authors, including Menkin,[5-7] Guest, Daly, Ware and Seegers,[8] Spector,[9] and Grob,[10-12] have attempted to explain the mechanism involved in the antiphlogistic action of trypsin. The concept evolved from their combined work, as expounded by Moser,[13] seems to be most logical and feasible. He suggested that migration of leukocytes and an increase in capillary permeability, which are the basic features of inflammation, are involved in response to proteoses, which are elaborated by the tissues, bacteria and leukocytes at the site of injury. Correlation of the data presented by Spector[9] and Grob[10-12] suggests the following explanation for the inhibitory action of trypsin on acute inflammation. The concentration of polypeptide is increased by the local action of proteolytic substances released from the leukocytes and the injured tissues, and this in turn stimulates the inflammatory reaction. On the other hand, daily intramuscular injection of trypsin causes an increase of antiproteolytic substance (antiprotease) in the serum, which in turn indirectly inhibits the production of polypeptides and thus controls the local inflammatory stimulus.

The use of such a powerful antiproteolytic agent as trypsin has been suggested for the treatment of a variety of diseases, not only for its thrombolytic action but also for its antiphlogistic and anti-edema effect. Its use consequently offers a new therapeutic approach to some very perplexing problems. Since certain pathologic features are predominantly present in all ulcers, no matter where the ulcers are situated, certain facts can be deduced by careful study.

### *Chymotrypsin*

Chymotrypsin, which is supplied as CHYMAR® aqueous for intramuscular injection, is an endopeptidase fractionated from the bovine pancreas by a modification of the method of Kunitz and Northrop.[14] Chemically, chymotrypsin is distinguished from trypsin by the peptide bonds it splits. It causes a reduction of edema, either by restoring fluid balance in the lymph and venous channels or by removing soft fibrin or inflammatory plugs, which hastens absorption by greatly increasing tissue permeability. It reverses inflammatory processes and consequently stops further necrosis of tissues. It thus provides an improved medium and enhances local conditions of repair and regeneration.[15]

### *Etiology of Peptic Ulcer*

Research regarding the cause of gastric and duodenal ulcer has been intensified during the past two decades, but it has not disclosed any single condition that is responsible for the development of the ulcer. Instead, the investigative work has only emphasized that several factors, working conjointly or consequentially, are responsible for the ulcer. Since the treatment of peptic ulcer is largely influenced by the cause of the ulcer, the physician should try to ascertain the cause of the ulcer in each patient.

*Psychic influences*—It cannot be stressed too strongly that the physician should make every possible effort to determine whether psychic stress might be responsible for the ulcer. It has been found that peptic ulcer is incident to and perpetuated or aggravated by significant stresses in the life situation.[16] In other words, persons with certain types of personalities are prime candidates for a peptic ulcer as a result of their inability to relieve tension and their overcontrol of emotions.[17]

*Hypersecretion of pepsin and hydrochloric acid*—The immediate cause of peptic ulcer is the corrosive action of hydrochloric acid as it presumably surpasses the diminished resistance of the gastric mucosa.[18] Peptic ulcers have been produced experimentally by the overproduction of hydrochloric acid or by interference with the neutralizing and buffering mechanism.[19] The role of hydrochloric acid in the formation of peptic ulcer is comparable to that of a catalyst in a chemical reaction. Without a catalyst, a chemical reaction cannot progress.

*Alteration of tissue resistance*—In experiments performed on dogs at Cornell University, Beal and Martin[20] found that peptic ulcer occurred in the stomach and duodenum but not in the mucosa of other parts of the in-

testine which was unaccustomed to gastric juice containing pepsin and hydrochloric acid. Although the results of their experiments are highly suggestive that there is some other factor which alters the resistance of the mucosa, hydrochloric acid remains an essential etiologic factor.

*Hypermotility and hyperirritability*—In the roentgenologic diagnosis of peptic ulcer, the stomach commonly is observed for evidence of hypermotility or hyperirritability. Several studies recently have been made to determine the effect of anticholinergic drugs on gastric motility and the doses of the drugs required to produce complete motor inactivity of the stomach. I wholeheartedly agree with Barowsky, Schwartz and Lister[21] that double or triple the recommended doses of these drugs must be administered to produce complete motor inactivity of the stomach.

*Smoking*—Smoking is an important etiologic factor, and, exasperatingly, it is one of the most difficult habits to combat. Like other authors, I have observed many cases in which smoking has had a detrimental effect on the healing of a peptic ulcer. It, therefore, was strictly prohibited in the cases which form the basis of this report.

*Alcoholic beverages*—The use of alcoholic beverages in any form is another important cause of peptic ulcer.

*Injudicious and irregular eating habits*—Injudicious or irregular eating habits also are an important etiologic factor. Many persons disregard thermal extremes, and thoughtlessly adhere to the daily use of some particular food, such as a bowl of "chili" or a "hot-dog" or salami sandwich, but completely disregard fresh vegetables, fruit, milk and other necessary foods which contain vitamins.

*Prolonged physiologic abuse*—Prolonged physiologic abuse, such as keeping extremely late hours without regard for normal rest, also injures the integrity of the gastric and duodenal mucosa.

### *Material and Method of Study*

While Chymar aqueous was being used in a case of stasis ulcer, an associated ulcerative colitis subsided unexpectedly. This suggested that this enzyme might be effective in a variety of disease conditions. It then was administered in six consecutive cases of severe ulcerative colitis. In all of these cases, medical treatment previously had been used for periods ranging from eight months to five and a half years, but it had produced only moderate improvement or no improvement at all. In one of these cases, two transfusions of whole blood had been necessary in the 13 months before the administration of Chymar aqueous was started. Complete healing occurred rapidly in all of these cases. In a period of more than three years, repeated proctoscopic examination has not revealed any evidence of recurrence of the colitis in any of the cases.

It then was believed that chymotrypsin might cause healing of peptic ulcer. Chymar aqueous, therefore, was administered in 10 cases of this disease. The results were just as satisfactory as they were in the cases of ulcerative colitis, and healing occurred just as rapidly. The drug subsequently was administered in 14 additional cases of peptic ulcer. In the next three years, it was used in conjunction with other medicaments in 54 additional cases of peptic ulcer. It, therefore, has been used alone or in conjunction with other medicaments in 78 cases of peptic ulcer, which have been divided into two groups.

*Group 1* includes 24 cases of gastric, duodenal or marginal ulcer in which Chymar aqueous was the only medicament used. Twenty-two of the 24 patients in this group of cases were men and two were women. The average age of the 24 patients was 40.5 years. In these cases, 5000 units of Chymar aqueous was injected into the gluteal muscle once a day for 21 days. During the next three to six weeks, 2500 units of Chymar aqueous was administered daily. Subsequently, 5000 units was administered three times a week for four to eight weeks in certain cases. No other medicament was used in this group of cases. A dietary regimen was maintained, and smoking was prohibited.

*Group 2* includes 54 cases in which Chymar aqueous was used in conjunction with other medicaments. Of the 54 patients in this group of cases, 46 were men and eight were women. The average age of the patients was 42.7

years. This group of 54 cases includes five cases which also are included in group 3, that is, the group in which the patients were treated by conventional methods without the use of Chymar aqueous. In these five cases, the patients were treated with Chymar aqueous and other medicaments after initial treatment without Chymar aqueous had failed to produce healing of the ulcer.

The patients in this group of 54 cases cannot be compared with the average ambulatory ulcer patient observed in the office or clinic. Most of the patients were confined to the hospital because of persistent or intractable bleeding or because of some obstructive phenomenon such as uncontrollable regurgitation or vomiting. In most of these cases, treatment by conventional methods had not been effective. In some of the cases, such drastic measures as daily intubation of the stomach had produced little if any improvement.

In addition to the administration of Chymar aqueous and PRO-BANTHĪNE® (propantheline bromide), treatment included the use of antacids, and the administration of COMPAZINE® (prochlorperazine) for its antiemetic action, for the control of psychic stress, and for the control of the urge and the irascibility resulting from the prohibition of smoking. An ambulatory type of ulcer diet, which included MERITENE® milk shakes, was used. Vitamin supplements also were used.

In addition to the 78 cases included in groups 1 and 2, the study included a control group of 26 cases (*group 3*) in which Chymar aqueous was not administered. Of the 26 patients in this group of cases, 23 were men and three were women. The average age of the 26 patients was 39.3 years. From 60 to 270 mg. of Pro-Banthīne was administered in divided doses in each 24 hours. In most of the cases in which intensive therapy with this drug was used, the patients were practically incapacitated insofar as gainful employment was concerned, and the size of the dose and the frequency of administration of the drug had to be adjusted for each patient.

Certain rigid criteria were used in the selection of the cases included in these three groups. In the absence of proof of intestinal hemorrhage, the presence of a peptic ulcer had to be proved by roentgenologic demonstration of a crater or niche.

Equally stringent criteria were used in evaluating the results of treatment. Complete cessation of signs and symptoms such as pain, obstructive phenomena and melena was not considered evidence of healing of the ulcer unless roentgenologic examination definitely demonstrated filling-in or repair of the crater or niche. Evidence of such healing had to be encountered repeatedly while the involved portion of the stomach or duodenum and the adjacent portion of the intestine were in a quiescent and nonirritable state. Insofar as it was possible, the roentgenologic studies were performed on the twenty-first, the ninetieth, the one hundred and twentieth and the one hundred and eightieth day.

### *Results*

*Group 1*—Cessation of all symptoms and complete healing of the ulcer occurred in 21 (87.5 per cent) of the 24 cases in which Chymar aqueous was the only medicament used. The average time required for the cessation of symptoms was 5.8 days, and the average time required for complete healing of the ulcer as disclosed by roentgenologic examination was 24 days. The period of follow-up observation in this group of cases ranged from 18 to 33 months, and the average duration of the period was 25.5 months. During the period of observation, the ulcer recurred in only three (12.5 per cent) of the 24 cases. In these three cases, the ulcer remained healed for an average of 8.2 months before it recurred.

Although the results were excellent in this group of cases, I do not wish to imply that all patients with peptic ulcer should be treated with Chymar aqueous alone. Additional therapy is indicated for acceleration of the relief of symptoms and for associated complications such as vomiting and bleeding.

The following case report will illustrate the result obtained in one of the 24 cases in which Chymar aqueous was the only medicament used.

*Case 1*—A policeman, aged 30 years, had had stomach trouble since the age of 18 years.

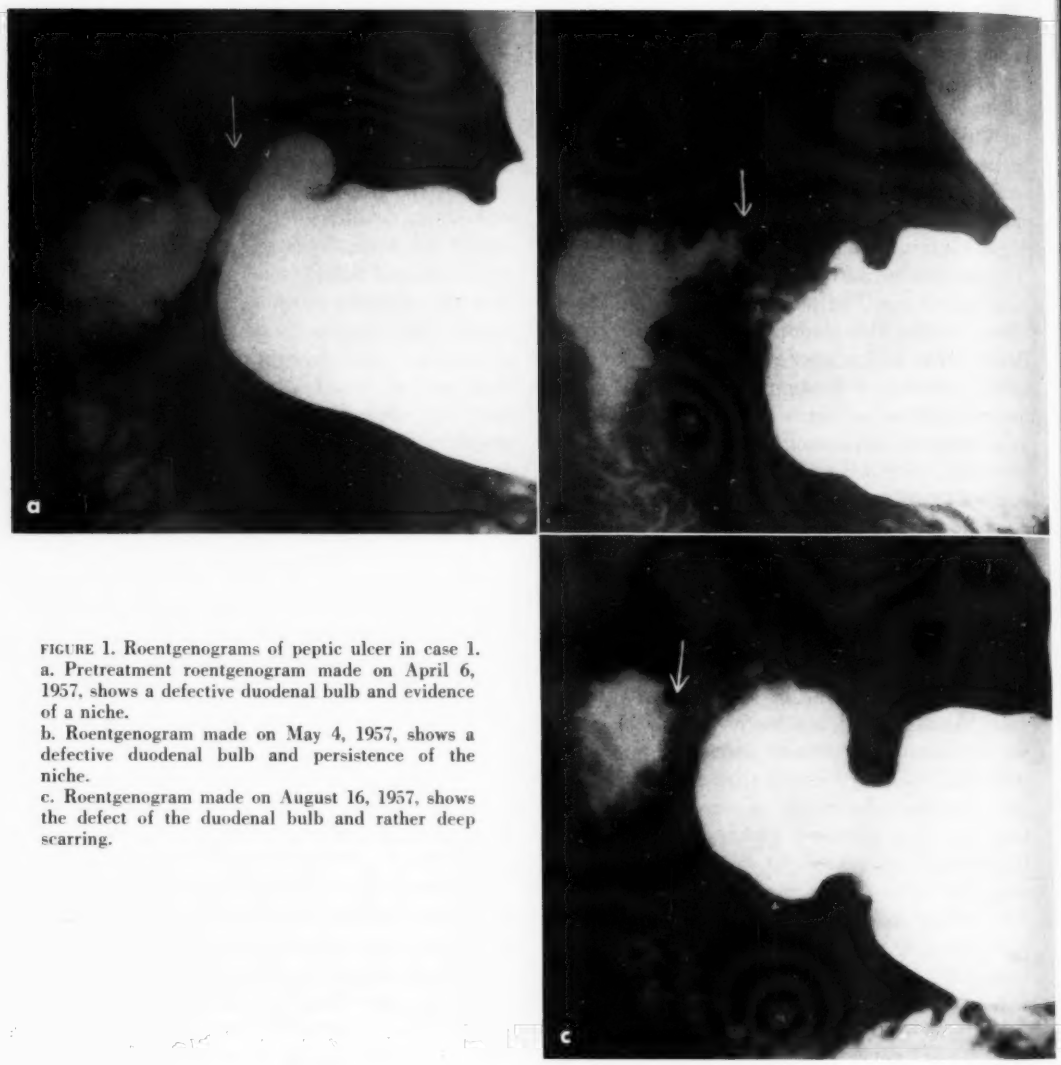


FIGURE 1. Roentgenograms of peptic ulcer in case 1.
a. Pretreatment roentgenogram made on April 6, 1957, shows a defective duodenal bulb and evidence of a niche.
b. Roentgenogram made on May 4, 1957, shows a defective duodenal bulb and persistence of the niche.
c. Roentgenogram made on August 16, 1957, shows the defect of the duodenal bulb and rather deep scarring.

When he was 22 years old, roentgenologic examination had disclosed a duodenal ulcer. The symptoms included dull, cramplike pain in the pit of the stomach, occasional nausea and vomiting, and headache. He usually was constipated. In April 1957, the pain became very severe, and the patient was hospitalized. Owing to his working conditions, the patient had been smoking about two packages of cigarettes a day, had been eating irregularly, and had been taking medicine only when reminded to do so by the occurrence of pain or distress. When treatment was started, the patient had a great deal of discomfort, and he was very miserable and irritable.

A roentgenogram made on April 6, 1957 revealed a defective duodenal bulb and evidence of a niche, which indicated the presence of an active duodenal ulcer (figure 1a). Chymar aqueous was administered daily by intramuscular injection, and smoking was prohibited. No other medicament was used. A

roentgenogram made on May 4, 1957 still revealed a marked defect of the duodenal bulb, and the niche persisted (figure 1b). The duodenal cap, however, was not as irritable as it had been at the time of the previous roentgenographic examination.

When the patient was questioned closely, he admitted that he had not stopped smoking cigarettes. Sedatives were used, and 15 mg. of Compazine was administered twice a day by the oral route. As a result of this medication, he was able to break the smoking habit in about two weeks. On May 27, 1957, roentgenographic examination revealed that the activity of the ulcer had ceased almost completely. A roentgenogram made on August 16, 1957 still revealed a defect of the duodenal bulb and rather deep scarring of the duodenum (figure 1c). It did not reveal any evidence of intestinal obstruction or activity of the ulcer. There has not been any recurrence of the ulcer.

*Group 2*—All of the symptoms disappeared and complete healing of the ulcer occurred in 49 (90.7 per cent) of the 54 cases in which Chymar aqueous was administered in conjunction with other medicaments. The average time required for the cessation of symptoms was six days, and the average time required for complete healing of the ulcer as disclosed by roentgenologic examination was 36 days. The average duration of the follow-up observation was 12.1 months. The ulcer never healed in two (3.7 per cent) of the 54 cases. In three (5.5 per cent) of the cases, the ulcer healed but recurred. The average time that elapsed between the completion of treatment and the recurrence of the ulcer in these cases was 10 months. The ulcer, therefore, either failed to heal or healed but recurred subsequently in five (9.2 per cent) of the 54 cases in this group. In view of the refractoriness of the ulcer and the exigent condition of most of the patients in this group of cases, the results were most heartening.

As previously stated, this group of 54 cases also includes five cases which are included in the control group (group 3). The patients in these five cases originally were treated with anticholinergic drugs, antacids, sedatives, antispasmodics and vitamins, but the ulcer failed to respond to the treatment even after the doses of the drugs had been altered and after various combinations of drugs had been used. Improvement occurred almost immediately after the intramuscular administration of Chymar aqueous was started. All symptoms disappeared, and roentgenologic examination revealed progressive and uninterrupted healing of the ulcer. In my opinion, the results obtained in these five cases are evidence of the healing properties of chymotrypsin.

The following case report will illustrate the results obtained in this group of cases.

*Case 2*—The patient in this case was a 35 year old dock worker. Gastrointestinal symptoms first had occurred in 1952, but the patient did not consult a physician until 1954. About the middle of 1955, the gnawing and burning sensation became more painful and discomforting. Heartburn and belching caused him to awaken nightly after he had slept for two and a half or three hours, and he had to use antacids and anticholinergic drugs liberally in order to obtain temporary relief.

A roentgenogram made on January 26, 1957 revealed the niche of a large ulcer on the upper third of the lesser curvature of the stomach (figure 2a). The ulcer had penetrated to a depth of almost three-fourths of an inch, but it appeared to be benign.

Chymar aqueous was administered without any other medicament. A roentgenogram made on February 23, 1957 revealed only a slight indentation on the lesser curvature of the stomach (figure 2b). An aerogram made on February 28, 1957 revealed a tiny niche which was one-eighth of an inch deep. It also revealed radiating gastric folds which were indicative of healing of the ulcer.

An operation had been contemplated, but it was deferred. A roentgenogram made on March 28, 1957 revealed almost complete healing of the ulcer (figure 2c). The niche was about one-sixteenth of an inch deep. The rest of the stomach and the duodenal cap were normal.

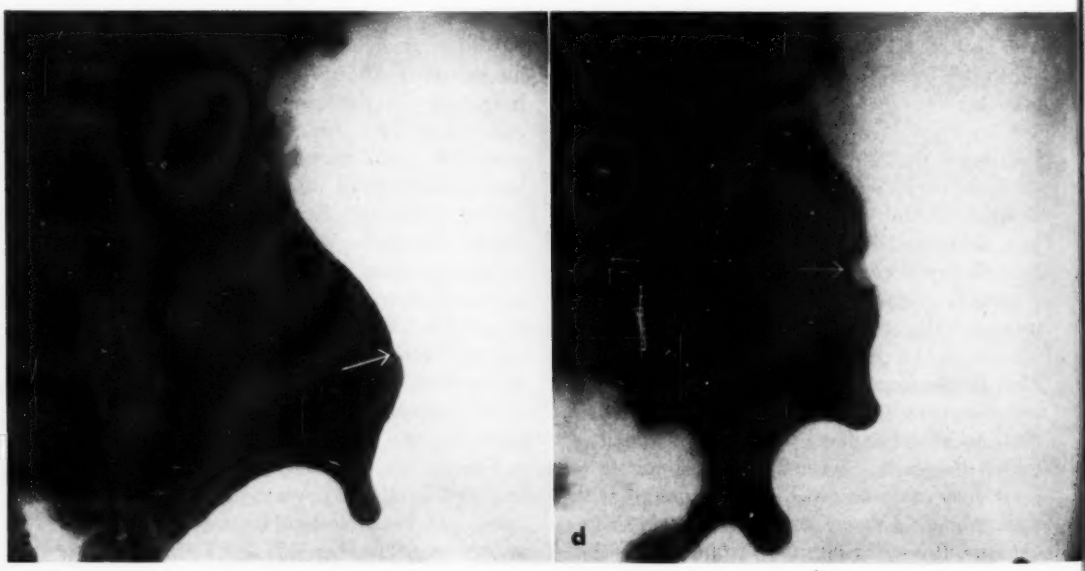
The patient then indulged in smoking, dietary indiscretions, the use of alcoholic beverages, and keeping late hours. A roentgenogram made on May 17, 1957 demonstrated

FIGURE 2. Roentgenograms of peptic ulcer in case 2.
a. Pretreatment roentgenogram made on January 26, 1957, shows a large niche on the upper third of the lesser curvature.

b. Roentgenogram made on February 23, 1957, shows only a slight indentation on the lesser curvature.

c. Roentgenogram made on March 28, 1957, shows that the ulcer is almost completely healed.

d. Roentgenogram made on May 17, 1957, shows evidence of reactivation of the ulcer, which apparently was due to smoking, dietary indiscretions, and the use of alcoholic beverages.



evidence of reactivation and deepening of the ulcer (figure 2d), which previously had healed almost completely. It is interesting to note how much erosion can occur in a period of only seven weeks. This can be easily discerned by comparing figures 2c and 2d.

Subsequently, Pro-Banthīne was administered in conjunction with Chymar aqueous. This treatment resulted in closure of the defect and complete cessation of the pain and distress.

*Group 3*—Cessation of all symptoms and complete healing of the ulcer occurred in 13 (50 per cent) of the 26 cases in which the patients were treated in the conventional manner, that is, without the use of chymotrypsin. The average time required for the cessation of symptoms in these 13 cases was 6.4 days, and the average time required for complete healing of the ulcer as disclosed by roentgenologic examination was 51.2 days. The average duration of the follow-up observation in the 26 cases in group 3 was 44.5 months.

In the 13 cases in which the ulcer recurred, the average time that elapsed before recurrence of the ulcer was 11.1 months. The use of larger doses of the respective drugs produced clinical relief and improvement in the appearance of the ulcer in eight of the cases in which the ulcer was refractory to treatment, but the ulcer could not be classified as healed on the basis of the criteria used in this study. As previously stated, Chymar aqueous was administered subsequently in five of these cases, and the use of this enzyme produced complete healing.

### *Untoward Reactions*

An indurative and hyperemic zone occasionally developed about the site of injection of Chymar aqueous. It was found that aspiration of Chymar aqueous into a hot syringe would cause a milky cloudiness of the Chymar aqueous. The use of a cold syringe reduced the incidence of local reactions.

Chymar aqueous was administered intramuscularly on 4,666 occasions in the 78 cases in groups 1 and 2, and only three (0.06 per cent) of the injections produced an allergic reaction. Two of these reactions, both of which occurred in men, were typical allergic reactions to drugs, and they were manifested by a dermal rash, hyperemia, urticaria and itching. One occurred at the time of the eighth injection and the other at the time of the forty-sixth injection. Both of these reactions were easily controlled with antihistaminic drugs. The third reaction, which occurred in a woman, was an anaphylactic shock reaction which was controlled by the intravenous administration of aminophylline, by the intravenous and intramuscular injection of antihistaminic drugs, and by the administration of ACTH.

### *Comment*

I believe that the most effective way of treating a refractory peptic ulcer is to administer chymotrypsin in conjunction with plain Pro-Banthīne or with Pro-Banthīne with DARTAL®. The blocking of the parasympathetic impulses by plain Pro-Banthīne or Pro-Banthīne with Dartal results in inhibition of the secretory and motor hyperactivity of the stomach. The enforced rest of the site of the ulcer certainly augments the physiologiclike healing produced by chymotrypsin.

### *Summary and Conclusions*

I believe that chymotrypsin offers a new approach to the treatment of peptic ulcer. Because of the excellent results obtained in 78 cases of peptic ulcer in which this enzyme was used alone or in conjunction with other medicaments, I strongly recommend its use as a most valuable adjunct in the treatment of this disease. It is possible that it may be the solution to the treatment of peptic ulcer.

The period of follow-up observation in this group of 78 cases admittedly is short, and it probably should be extended. It is hoped that the results of this study will stimulate more widespread interest in the use of this enzyme. It also is hoped that other studies may be made for the purpose of confirmation.

The concomitant use of anticholinergic drugs and tranquilizing agents enhances the healing properties of chymotrypsin by affording rest to the involved portion of the stomach and by relieving psychic stress. The concomitant use of such drugs is recommended.

## ACKNOWLEDGMENTS

I wish to acknowledge the diligent cooperation of Dr. N. Zeitlin and the untiring efforts of Claire Race, R.N. and Della Bloomenthal. I also am indebted to Dr. R. A. Hecht of the Armour Pharmaceutical Company for the generous supply of Chymar aqueous used in this study. Finally, I wish to express appreciation to my many colleagues for their cooperation in the referral of patients with peptic ulcer.


## REFERENCES


1. Tillett, W. S. and Garner, R. L.: Fibrinolytic activity of hemolytic streptococci. J. Exper. Med. 58:485 (October) 1933.
2. Innerfield, I., Angrist, A., Schwarz, A. and Ruggiero, W.: Intravenous trypsin: Its effects upon intravascular thrombi and the acute reaction. S. Forum, 1952, p. 526.
3. Fisher, M. M. and Wilensky, N. D.: Parenteral trypsin in peripheral vascular and thromboembolic diseases. New York J. Med. 54:659 (March 1) 1954.
4. Golden, H. T.: Intramuscular trypsin; its effect in 83 patients with acute inflammatory disorders. Delaware M. J. 26:267 (October) 1954.
5. Menkin, V.: Studies on inflammation. J. Exper. Med. 67:129 (January) 1938.
6. *Ibid.*, p. 145.
7. *Ibid.*, p. 153.
8. Guest, M. M., Daly, B. M., Ware, A. G. and Seegers, W. H.: Study of antifibrinolysin activity in plasmas of various animal species. J. Clin. Invest. 27:785 (November) 1948.
9. Spector, W. G.: Role of some higher peptides in inflammation. J. Path. & Bact. 63:93 (January) 1951.
10. Grob, D.: Antiproteolytic activity of serum. J. Gen. Physiol. 26:405 (March) 1943.
11. *Ibid.*, p. 423.
12. *Ibid.*, p. 431.
13. Moser, K. M.: Intramuscular injection of trypsin; its value as a thrombolytic and anti-inflammatory agent. New England J. Med. 256:303 (February 14) 1957.
14. Northrop, J. H., Kunitz, M. and Herriott, R. M.: Crystalline Enzymes. Ed. 2. New York, Columbia University Press, 1948, p. 352.
15. Pepi, J. F.: Treatment of peptic ulcer by use of intramuscular trypsin. Am. J. Gastroenterol. 26:582 (November) 1956.
16. Wolf, S.: Summary of evidence relating life situation and emotional response to peptic ulcer. Ann. Int. Med. 31:637 (October) 1949.
17. Kraines, S. H.: Psychiatric factors in therapy of duodenal ulcer. Illinois M. J. 110:157 (October) 1956.
18. Kirsner, J. B.: Current status of therapy in peptic ulcer. J.A.M.A. 166:1727 (April 5) 1958.
19. Oliver, J. V.: Effect of vagotomy on development of the Mann-Williamson ulcer in the dog. Arch. Surg. 55:180 (August) 1947.
20. Beal, J. M. and Martin, K. A.: Nervous and hormonal influences in peptic ulcer. S. Clin. North America, April 1958, p. 385.
21. Barowsky, H., Schwartz, S. A. and Lister, J.: New approach to management of peptic ulcer by inducing sustained gastric inactivity. Am. J. Gastroenterol. 24:533 (November) 1955.



1959

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Nov. 2-5 Palmer House Chicago, Illinois

**New Anesthetics: Their Evaluation and Possible Misuse**

This discussion will cover the usefulness, indications and contraindications and deleterious side effects of the new inhalants and intravenously administered and preanesthetic medicaments. Up-to-date knowledge concerning older drugs and technics of administration will be considered, and the handling of complications will be stressed.

JOHN ADRIANI, M.D.

Professor of Surgery, Tulane University School of Medicine, and Professor of Pharmacology and Clinical Professor of Surgery, Louisiana State University School of Medicine, New Orleans

# CLINICOPATHOLOGIC CONFERENCE

## Report From Veterans Administration Hospital, Hines, Illinois

*Edited by William J. Gillesby, M.D., Assistant Chief, Surgical Service*

### *Case Report*

A 41 year old Negro drugstore porter was admitted to Hines Veterans Administration Hospital for the first time on July 25, 1958. He had a three week history of pain in the toes of both feet and swelling of both ankles, followed by arthralgia which began in the ankles and subsequently spread to the wrists, shoulders and neck. The pain in the joints became so severe that the patient was barely able to move his neck or shoulders. On admission, the severe pains had disappeared and only some soreness remained in the joints.

In 1952, this patient had shortness of breath, edema of the ankles, and occasional nocturnal paroxysmal dyspnea, for which he was hospitalized elsewhere. A diagnosis of rheumatic heart disease was made, and he was told that he had several cardiac murmurs. The patient did not work for nine months following discharge from the hospital; then he gradually started doing light work. However, he continued to have occasional edema of the ankles, shortness of breath, and nocturnal dyspnea. The arthralgia was noted for the first time three weeks before the present admission. The patient stated that he had had orally administered penicillin continuously since 1952. In 1948, while hospitalized for evaluation of multiple hammer toes, he was told for the first time that he had a cardiac murmur. He denied ever having had rheumatic fever as a child or while in service, and he had never noticed any subcutaneous nodules or skin rashes. In 1938, he had pneumonitis involving the left lung, and since 1940, he had had occasional attacks of knifelike precordial pains. These pains were nonradiating; they occurred at any time and lasted from a few minutes to several hours. The patient said that the pains had seemed worse during the time just prior to his coming to Hines. Approximately two weeks before his present admission, a cough developed; he had two episodes of hemoptysis on the same day, with no subsequent recurrence. He slept on two pillows at night.

This review includes only the positive findings of the physical examination of this patient. On admission, he was well developed, well nourished, warm to the touch, and in no acute distress. His temperature was 101° F., pulse 72, blood pressure 140/70, and respirations 18. The lungs were clear. The heart had normal sinus rhythm with an even and regular rate. The $A_2$ sound equaled the $P_2$ sound, with accentuation of the second sound heard best over the base of the heart. A grade 3 blowing

systolic apex murmur, with radiation into the axilla, was noted; a grade 3 diastolic apex rumble and a grade 3 systolic aortic murmur also were present. A systolic thrill was heard over the apical area, with radiation into the left axilla. A systolic thrill heard over the base had no apparent radiation. The left border of cardiac dullness was enlarged to the left. Other positive physical findings on admission included small, easily movable cervical, axillary and inguinal lymph nodes and a slight trace of pedal edema.

*Hospital course*—Since the low-grade fever and physical and laboratory findings were referable to cardiac and renal disease, the patient was placed on a therapeutic regimen which included digitoxin, tetracycline, phenobarbital, mercaptomerin sodium, acetylsalicylic acid, aluminum hydroxide gel, erythromycin and sulfisoxazole. When urine culture demonstrated hemolytic *Staphylococcus aureus*, coagulase positive, nitrofurantoin was given because of the sensitivity of the organism to that drug. However, in spite of the treatment, the patient's fever continued to rise, spiking daily to approximately 101 or 102° F. and then returning to near normal at night. On August 28, a determination of purified protein derivative No. 2 was done and read in 48 hours as negative. Nevertheless, since there was the possibility of an overwhelming acid-fast infection, the patient was started on antituberculotic therapy, which consisted of streptomycin and isoniazid.

During this time, the patient complained of soreness in his mouth. An ear, nose and throat consultant noted acute ulcerations on the roof of his mouth. These were treated with gentian violet and gargles. The ulcers disappeared, but the patient continued to have some difficulty in swallowing; however, no reason for this dysphagia could be determined on examination. When he had been receiving antituberculotic therapy for approximately eight days, the patient's fever decreased and he remained essentially afebrile until he died. On September 4, he was started on 20 million units of penicillin K every eight hours around the clock; however, he died the following day.

*Laboratory data*—On July 25, x-ray examination revealed that the patient's chest was essentially normal. The posteroanterior and lateral views showed minimal elevation of the left hemidiaphragm and some prominence of the left ventricle. Calcifications were seen in and about both hili.

An esophagram was made and gastrointestinal and small bowel series were done on August 18. Other than exhibiting a small diverticulum near the coryna, the esophagus was normal. An impression on the lesser curvature of the stomach suggested a possible enlargement of the left lobe of the liver. The stomach and duodenal bulb and loop were normal. There was no abnormality of the jejunum or ileum.

On August 27, a posteroanterior x-ray of the chest showed normal findings, with no evidence of tuberculosis.

On July 25, the patient showed no reaction to a routine flocculation test. The ASO titer on July 28 was 12 units; on August 22, it was 625 units. Results of other tests performed on July 28 were: latex precipitation and precipitation test for lupus erythematosus, negative; heterophils, negative; multiple agglutinations of typhoid O and H, *Proteus* OX-19, *Brucella* and paratyphoid A and B, negative. Spinal fluid on August 27 was nonreactive.

On July 26, a sputum culture showed alpha and beta hemolytic streptococci and *Neisseria catarrhalis*; no organisms were seen in a blood culture. A sputum smear on July 27 revealed no acid-fast bacilli. Hemolytic *Staph. aureus*, coagulase positive, was seen in throat and urine cultures on August 4; the latter culture also showed *Streptococcus faecalis*. No organisms were seen in a culture of urine from the right kidney on August 11 or in a spinal fluid smear on August 27. Hemolytic *Staph. aureus*, coagulase positive, and *P. morganii* were revealed in a prostatic fluid culture on August 14. Urine cultures on August 12 and on September 2 showed *P. morganii* and *P. rettgeri*, respectively.

Other tests and results were as follows: July 28, C-reactive protein, negative; August 8, urea clearance, 53 per cent; August 18, sickle cell preparation, negative; August 22, reticulocyte count, below 0.1 per cent. On August

TABLE 1
LABORATORY DATA

| TESTS | DATES | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 7/25 | 7/27 | 7/28 | 7/31 | 8/4 | 8/18 | 8/28 | 8/29 | 9 1 | 9/2 | 9/3 |
| *Urinalyses* | | | | | | | | | | | |
| Specific gravity | 1.020 | | | 1.020 | | 1.005 | 1.008 | | | | |
| Albumin | 4 plus | | | 4 plus | | 4 plus | 4 plus | | | | |
| Albumin (mg. per 100 cc.) | 750 | | | 600 | | 200 | 300 | | | | |
| White blood cells | Numerous | | | 4-6 | | 6-8 | Few | | | | |
| Red blood cells | Numerous | | | 30-35 | | 18-25 | | | | | |
| Cells | Few epithelia | | | Few epithelia | | Few epithelia | Few epithelia | | | | |
| Casts | Granular and pus cells | | | Few bacteria | | 6-10 granular occult pus cells | Amorphous phosphorus crystals | | | | |
| Bence Jones protein | | | | | | | | | | | Negative |
| *Hematology* | | | | | | | | | | | |
| Hemoglobin | | | 14.5 | | | | | 10.5 | 12.0 | | |
| Red blood cell count (millions) | | | | | | | | | 4.2 | | |
| White blood cell count | | | 4.3 | | | | | 5.0 | 9.0 | | |
| Neutrophils | | | 72 | | | | | 87 | 58 | | |
| Lymphocytes | | | 28 | | | | | 10 | 40 | | |
| Eosinophils | | | | | | | | 3 | 2 | | |
| Sedimentation rate | | | 18 | | | | | 20 | | | |
| Hematocrit | | | 44 | | | | | 33 | 39 | | |
| *Chemistry* | | | | | | | | | | | |
| Transaminase | | 25 | | | | | | | | 945 | |
| Nonprotein nitrogen | | | 32.7 | | | | | 58.2 | | | |
| Glucose | | | 84 | | | | | | | | |
| Alkaline phosphatase | | | 2.1 | | | | | 5.7 | | 9.1 | |
| Protein | | | 5.9 | | | | | | | 5.3 | |
| Albumin | | | 3.4 | | | | | | | 2.2 | |
| Globulin | | | 2.5 | | | | | | | 3.1 | |
| Thymol turbidity | | | 4 units | | | | | | | | |
| Cephalin-cholesterol flocculation | | | | | | | | | | | 3 (24 hr.)<br>4 (48 hr.) |
| Sodium | | | | | | | | | | 135 | |
| Potassium | | | | | | | | | | 4.9 | |
| Carbon dioxide-combining power (mEq.) | | | | | 33.3 | 28.5 | | | | 20.4 | |
| Chloride (mEq.) | | | | | 93 | 91 | | | | 90 | |
| Cholesterol | | | | | 112 | | | | | 193 | |
| Esters | | | | | 75 | | | | | 90 | |
| Bilirubin | | | | | Less 0.5/0.15 | | | | | | |

Prothrombin time determination on August 21 was 13 seconds (100 per cent).

27, examination showed the spinal fluid to be clear, with no cells; sugar was 42, chloride 122, protein 34, and colloidal gold 0012110000.

An electrocardiogram on August 19 showed an abnormal tracing, with nonspecific ST-T wave changes suggestive of early left ventricular strain. On September 4, the electrocardiographic tracing also was abnormal, showing nonspecific T wave changes which were not diagnostic. It showed a faster rate and further changes away from normal than were seen in the previous tracing. Other laboratory data are summarized in table 1.

### *Discussion*

DR. JAMES A. CAMPBELL (chairman, department of medicine, Presbyterian-St. Luke's Hospital, Chicago): This patient's illness covered a span of 20 years, with a final acute episode of only a few months' or a few weeks' duration. I would like to discuss the protocol in this case from three viewpoints: (1) the clinical management, which indicated that during his final illness the patient was believed to have had subacute bacterial endocarditis; (2) the retrospective review, which one might make at any time; and (3) the clinicopathologic aspects, which usually are more abstruse than are the other two.

When this patient was examined in 1948, he was told that he had a cardiac murmur. Ten years previously, he had had pneumonitis, with episodes of knifelike pains two years later, which might have been caused by pleuritis, pericarditis or pericardiopleuritis. In 1948, he had symptoms suggestive of rheumatic fever, and this disease was diagnosed in 1952. The diagnosis and the subsequently administered prophylactic penicillin seem perfectly logical.

The description of the murmurs in this patient was not sufficiently graphic to tell whether or not damage to the heart involved one or more valves. At the time of the last admission, there was evidence of a systolic murmur and a diastolic murmur at the apex, a systolic murmur at the base, and a systolic thrill at the apex. Had a thrill been felt at the base in systole or at the apex in diastole, I would be tempted to state that this patient had rheumatic heart disease with aortic stenosis, with mitral stenosis and insufficiency. I would have been concerned had the right cardiac border of dullness been percussed more to the right, because I think that we all are trapped into thinking that the right side of the heart (that is, enlargement of the right ventricle) may be percussed to the right rather than anteriorly. The right ventricle is really the anterior ventricle, and increased retrosternal dullness gives physical diagnostic evidence of right ventricular enlargement. Indeed, we may find enlargement of the left border by percussion, because the enlarged right ventricle pushes the left ventricle laterally and toward the axillary line.

I am dwelling on the size of the ventricle and the nature of the murmurs and the thrill because the laboratory data showed that on fluoroscopy the left ventricle rather than the right ventricle seemed to be enlarged. This finding also makes it seem as though the systolic thrill would have been felt at the base rather than at the apex, because with slight enlargement of the left ventricle we should have more evidence of either mitral insufficiency or aortic stenosis. In a positive diagnosis of mitral stenosis, there should be either roentgenographic or fluoroscopic evidence of enlargement of the right ventricle. Furthermore, there is no mention in the protocol of electrocardiographic evidence of enlargement of the right ventricle. One might be tempted to explain the episodes of hemoptysis, which this patient had a few weeks prior to his last admission, on the basis of small pulmonary emboli, which would more likely be seen in mitral stenosis than in aortic stenosis.

I think that this patient probably had underlying rheumatic heart disease, which became more acute, along with the arthralgia and the pain which he described as having started three weeks before his last admission. There also was evidence of both aortic and mitral valvular disease, which was not well substantiated or documented by the laboratory data. Because the patient was febrile and because he had underlying heart disease, subacute bacterial endocarditis was suspected. As I mentioned earlier, the protocol seems to indicate that he was treated for subacute bacterial en-

d>carditis. This diagnosis could have been established only by multiple examinations of the patient's heart to see whether or not there was any shift or change in the character of the murmurs as his illness progressed. Unfortunately, there were no positive blood cultures mentioned in the protocol. I noted that the blood cultures originally were taken on three successive days. A more effective diagnostic procedure is to take a lot of blood in a short period, so that a volume effect rather than a peak effect is achieved. It also would have been particularly helpful to have had a detailed description of the eyegrounds, in which examination should have been made for little emboli and petechiae. Multiple tourniquet tests also are helpful in patients with subacute bacterial endocarditis. These can be performed readily while one is taking the blood pressure.

I do not quite understand why this patient was treated with mercurials, as it was not indicated that he was in heart-failure at any time during his hospitalization. We might properly turn our attention to the kidneys to see what evidence there was of subacute bacterial endocarditis. At no time was the urine free of showers of red cells. The concentration seemed to range from diluted urine to heavily concentrated urine. Varying degrees of proteinuria were seen, but the persistent showering of red cells was good evidence of focal embolic phenomena consistent with subacute bacterial endocarditis.

There also was hematologic evidence consistent with subacute bacterial endocarditis. When this patient was admitted to the hospital, the hemoglobin was within satisfactory limits, but during the final days of his illness the hemoglobin had dropped to 9 gm. This, together with the underlying rheumatic heart disease, fever, showers of red cells in the urine, and a progressive development of anemia, places subacute bacterial endocarditis at the top of the list of possible diagnoses.

Why do I seem to dwell so much on what is perfectly obvious? We owe it to every patient to consider the treatable diseases first in differential diagnoses. It is not difficult to consider the untreatable diseases or those which are difficult to treat and to confirm our pessimism at autopsy. However, if we do not seriously consider a treatable disease and press toward treating it, our complacence at being satisfied clinicians in the postmortem room is ill deserved.

The second phase of this discussion is concerned with a retrospective review. Those managing the patient seriously considered the diagnosis of subacute bacterial endocarditis, and I believe they were correct in so doing. In reviewing the protocol, it became obvious to me that it would be remiss not to diagnose disseminated lupus erythematosus. It is sometimes easier to work backward from the disease than to consider the symptoms and then arrive at the diagnosis. This is what I did, using an old edition of Cecil, which contains a description of disseminated lupus erythematosus that practically describes this patient. It states that when a patient has an arthralgia which resembles an obscure rheumatoid arthritis or rheumatic fever, along with persistent hematuria which cannot be ascribed to acute glomerulonephritis, it must be diagnosed as disseminated lupus erythematosus. I think this is a good formula to follow. This patient had arthralgia 10 years ago and again before he died. It was not determined whether or not rheumatoid arthritis was present; however, the x-rays showed little evidence of this disease. I think we should seriously consider the diagnosis of disseminated lupus erythematosus in this patient.

The third category I wish to discuss is the expected clinicopathologic diagnoses. In this regard, I would like to mention the possibility of a sarcoid. Arthralgia and renal findings which would give a clinical pattern such as seen in this patient are consistent with this condition. Furthermore, both a sarcoid and lupus erythematosus will give some bizarre neurologic findings. I am going to emphasize particularly the presence of dysphagia, which was mentioned in the protocol, despite the mucous lesions, which are more typical of lupus than they are of any of the other conditions considered. Although these lesions cleared, the patient had persistent dysphagia. I must suggest that the brain should be examined very carefully to see whether or not

there is evidence of polyarteritis or sarcoid-like lesions which would give a neurologic basis for this dysphagia.

An outside diagnosis of sarcoid is supported by the fact that this man's tuberculin reaction was negative, although on at least one occasion calcium was seen in the chest x-rays. In addition, tuberculosis was never diagnosed, although it was suspected. Multiple sputum smears were done to determine whether or not acid-fast bacilli were present, but none were found.

Another diagnostic possibility which should be mentioned is periarteritis nodosa, although no lumps were seen. Tuberculosis also should be considered in spite of the negative data. Careful examination for tuberculosis was conducted, including a lumbar puncture to ascertain whether or not the patient had tuberculous meningitis. At no time was the spleen mentioned; this is always disconcerting when you are looking for some of these borderline diseases. The final transaminase determination was fantastically elevated; however, I do not think that this patient had acute necrosis of the liver or anything other than heart-failure. Heart-failure could be consistent with bacterial endocarditis and could readily produce pulmonary infarction, providing the vegetations were on a tricuspid valve. However, there was no evidence of this, unless the systolic thrill could be ascribed to the tricuspid rather than to the mitral area. This condition also could be resistant to therapy, as mentioned, if the vegetations were too deeply involved in the aortic valve.

In considering the diagnosis of disseminated lupus erythematosus, I would like to mention that the patient could have had this disease without the presence of bacterial endocarditis. He could have had Libman-Sacks disease, a type of endocarditis in which the emboli would be more benign; they would not be infected, but they might well give the clinical picture which was presented here and exist until the patient died.

I believe that I would have treated this patient as he was treated—for subacute bacterial endocarditis. I think that he probably had disseminated lupus erythematosus. I do not believe that he had tuberculosis, and I doubt that he had sarcoidosis or acute or chronic glomerulonephritis.

RADIOLOGIST: The x-ray of the chest taken on August 7 showed that the lung fields were clear. The heart was enlarged and the silhouette suggested some enlargement of the left ventricle. There was a slight tortuosity of the aorta. Findings in the remainder of the examination and in an intravenous pyelogram were within normal limits.

In the cardiac series, the anteroposterior view showed the esophagus well in line; however, a lateral view showed that the esophagus may have been slightly displaced posteriorly. Although there was no evidence of left auricular enlargement, the possibility of left ventricular enlargement was suggested. A right anterior oblique view also showed no evidence of left auricular enlargement; however, since there was a slight displacement of the esophagus posteriorly, I would say that the heart was enlarged above the limits of normal, with some enlargement of the left ventricle.

DR. MYRON RUBNITZ (chief of laboratory service): Because of the unusual clinical history and course, as well as the many noncontributory laboratory tests, there was great interest at the necropsy table as to what the pathologic findings in this patient would be. As is sometimes the case, the gross examination of the organs showed remarkably little except for the findings in the heart, lungs and lymph nodes.

The heart was enlarged and weighed 400 gm. There were a few petechial hemorrhages over the epicardial surface. The most significant findings were in the mitral and aortic valves. Both showed small, gray, firm verrucae (figure 1), which measured from 2 to 4 mm. in diameter. On the mitral valve the verrucae were along the line of closure, while they appeared between the cusps of the aortic valve. The myocardium showed small areas of fibrosis. The microscopic sections verified the cardiac lesions as those of atypical vegetative endocarditis or Libman-Sacks disease. Sections through the verrucae showed masses of eosinophilic-staining material blending into focal areas of a deeply basophilic substance,

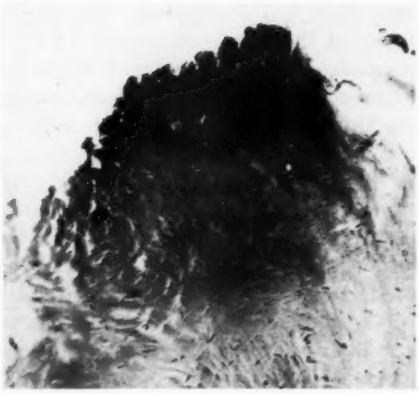


FIGURE 1. Vegetative endocarditis of the mitral valve.

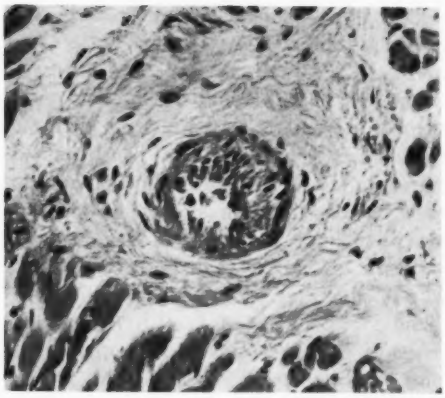


FIGURE 2. Fibrinoid deposition in wall of coronary arteriole.

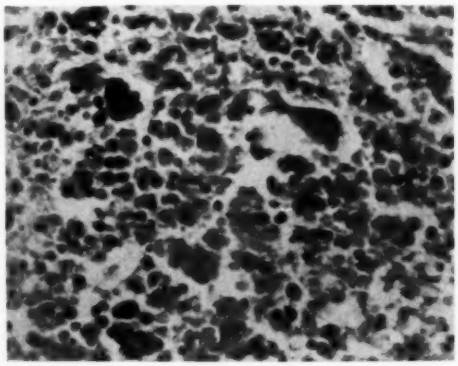


FIGURE 3. Hematoxylin-staining bodies in lymph node.

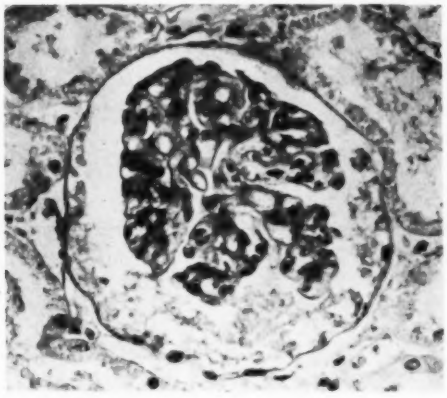


FIGURE 4. "Wire looping" of lupus erythematosus in kidney glomeruli.

the hematoxylin-staining bodies so characteristic of systemic lupus erythematosus. The true nature of the verrucae, in contradistinction to vegetations, was determined when proliferated, but intact endocardium was found lining the surfaces. Vegetative endocarditis ordinarily shows masses of fibrin, inflammatory cells and often bacteria overlying the endocardium. The verrucae in this case were cultured, and no bacteria were found. In the myocardium, the walls of many small arterioles contained varying amounts of the eosinophilic material seen in the valves (figure 2). This is the so-called fibrinoid degenerative material which many recent cytochemical studies have shown to be not an alteration of collagen, as first de-

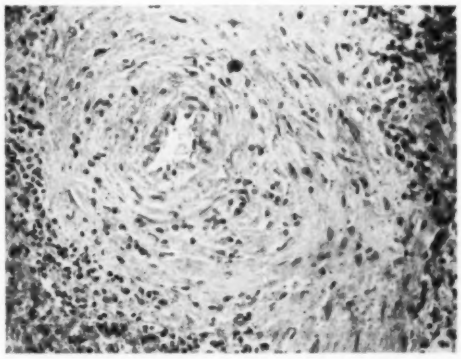


FIGURE 5. Periarterial fibrosis in spleen.

scribed, but associated with a change in desoxyribonucleic acid metabolism.

Grossly, the lungs showed areas of consolidation at the bases, and on microscopic examination revealed an unusual pattern of pneumonia. Many of the alveolar walls were destroyed, and these focal areas were infiltrated by mononuclear cells suggesting Friedländer's pneumonia. This was borne out when a culture of lung revealed growth of *Klebsiella pneumoniae*.

The grossly altered lymph nodes, which were soft and necrotic, also showed destruction of architecture microscopically. The most striking find, however, was numerous small and larger hematoxylin-staining bodies (figure 3). Many of the small arterioles also showed deposition of fibrinoid material in their walls.

The kidneys, although grossly involved, displayed more microscopic findings pathognomonic of lupus erythematosus (figure 4). Primarily, there was the typical "wire looping" of many of the glomeruli, caused by the accumulation of fibrinoid material in the basement membranes of the glomerular capillary loops. Other renal vessels also showed some of this eosinophilic material.

On microscopic examination, the central and penicilliary arteries of the spleen also demonstrated changes typical of periarterial fibrosis (figure 5). In these lesions, the vessels showed concentric layers or rings of collagen in which were seen fibroblasts and inflammatory cells, resulting in marked architectural changes. The liver showed only scattered foci of necrosis, with no vascular changes.

The anatomic diagnosis in this patient was disseminated lupus erythematosus which involved the heart, kidneys, spleen and the lymph nodes, with Libman-Sacks disease (atypical vegetative endocarditis) and Friedländer's pneumonia.


1959

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Nov. 2-5 Palmer House Chicago, Illinois

Indications for and Results of Ligation of the Inferior Vena Cava for Thrombo-embolic Disease

Venous ligation in thrombo-embolic diseases is limited to cases of phlebothrombosis and suppurative thrombophlebitis. Although ligation of superficial veins is sometimes satisfactory, increasing evidence shows that ligation of the inferior vena cava is preferable in most instances. Indications for and technic and results of vena caval ligation will be discussed.

ALTON OCHSNER, M.D.

Professor of Clinical Surgery, Tulane University School of Medicine, New Orleans

# A Training Program in Clinical Pharmacology

LOUIS LASAGNA*

*The Johns Hopkins University School of Medicine, Baltimore*

*Recognizing the need for trained clinical investigators experienced in evaluating drugs, The Johns Hopkins University School of Medicine has instituted a fellowship program for training physicians in clinical pharmacology.*

*The program is flexible but encompasses certain basic requirements for qualification of applicants.*

*The course and training are discussed and the prerequisites and objectives described.*

LOUIS LASAGNA

THE evaluation of drugs in the human suffers at present from a paucity of sophisticated and critical investigators. This need is perhaps most acutely recognized by the pharmaceutical industry, which must find experienced and able investigators to evaluate compounds in hospital settings and find similar personnel for their own departments of clinical investigation, there to serve as important liaison men between the basic science units of industry and the medical profession. A recent survey[1] suggests that most professors of medicine do not as yet appreciate fully the need for having clinical pharmacologists in their own departments.

After many years of discussion of this problem and of ways to implement a plan to increase the supply of clinical pharmacologists, the American Drug Manufacturers Association, through its Medical Section, decided in June 1956 to support a program to train physicians in clinical pharmacology at The Johns Hopkins University School of Medicine. This grant was originally for a total of $7500 per year and was awarded to the Division of Clinical Pharmacology. Approximately a year later, the Pharmaceutical Manufacturers Association (successor to the American Drug Manufactur-

*Departments of Medicine (Division of Clinical Pharmacology) and of Pharmacology and Experimental Therapeutics, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

ers Association and American Pharmaceutical Manufacturers Association) decided to continue this support, raising the yearly grant to $10,500. This is to be used in part for salary of a fellow, and in part to meet additional expenses incurred by his research. Because of the interest engendered by announcements of this program, it was thought advisable to describe the program in detail for those interested in its development and the mechanics of its execution.

Ideally, the fellowship is aimed at the further training of an individual who has had experience in both clinical matters and pharmacologic experimentation. It is our feeling that a minimum of several years of postmedical school clinical training is a prerequisite to efficient functioning in clinical pharmacologic investigation. Internship and residency training is necessary for the development of the clinical skills required to plan and execute experiments in human disease. Clinical naïveté and lack of appreciation of the natural history of disease and of hospital and outpatient procedures are serious handicaps to the proper performance of clinical pharmacology. We believe that in the absence of the minimum hospital training described, an interested candidate is best advised to take the time off to get such training before entering into our fellowship training program. The second qualification, that of having had some training in a pharmacology laboratory, is unquestionably a good principle, but in practice will be less easily achieved. For some time to come, compromises will probably have to be made in regard to this requirement by those desiring to set up such training programs. It is hoped that someday there will be an ample supply of clinicians who will also have been trained in a good pharmacology laboratory, but at the moment such a supply is obviously not at hand.

The training of a fellow in clinical pharmacology at our institution is conducted along several lines. This program is purposely flexible, so as to take into account the candidate's particular past training and interests. For many fellows, we believe that attendance at the course lectures conducted by the Department of Pharmacology will be a worthwhile pursuit during the first year of training. This will serve to bring the candidate up to date in the broad field of pharmacology and experimental therapeutics. We further believe that most such candidates will profit by attending a general statistics course, which in our case would be chosen from among those offered by the Department of Biomathematics in the Schools of Medicine and Hygiene. The appreciation of basic statistical concepts and at least a working knowledge of simple statistical technics are unquestionably of considerable importance in clinical pharmacology.

Another section of the training program concerns the trainee's participation in certain medical meetings at the institution. In our case, this would mean attendance at the weekly medical staff rounds and therapeutics conferences and the clinicopathologic conferences. We believe that this minimum of participation in the most important clinical events occurring at the institution is necessary so that the fellow shall not lose contact with the broad area of medicine. In addition, we consider it desirable for the fellow to work part of each week in one outpatient clinic (for example, in our Cancer Chemotherapy Clinic) or to visit on the wards. These assignments are important not only for continued training in general medicine, but also for the opportunity they provide to engage in teaching students and house staff. It is anticipated that no small part of a clinical pharmacologist's duties will be in the nature of teaching, be it of other potential clinical investigators, house staff, pharmaceutical firm personnel, etc. Along these same lines, our fellows are encouraged to participate in the planning and conduct of the therapeutics conferences organized by our division.

The final aspect of the program, which is less easily described, is the keystone of the entire plan. This concerns the planning of and participation in actual clinical trials. It is our firm conviction, after a number of years of experience in this area, that courses and reading cannot substitute for active participation in clinical trials. The subject matter of a particular clinical trial is less important than the actual planning and execution. We have utilized investigations of antibacterial chemo-

therapy, analgesics, hypnotic drugs, psychopharmacologic agents and antitumor drugs, for example. Each one of these has allowed the development of a protocol covering the principles of careful planning, randomization of patient material, concurrent comparison, placebo or standard therapy controls, and statistical evaluation of data. Naturally, the broader the experience that a fellow can obtain in several areas of drug evaluation, the better prepared he will be for the general function of pharmacologic measurement in man. Nevertheless, there is a certain basic rationale and procedure underlying most clinical trials which can be grasped reasonably well by participation in a few well-devised experiments.

One additional consideration deserves mention. I refer to the presence of laboratory facilities to pursue problems that arise out of clinical research. The study of drugs usually proceeds from the laboratory to the clinic, but frequently findings in man pose questions most easily (or perhaps only) answerable by studies in lower animals or in vitro. To render such research impossible by categorically declaring nonclinical research "out of bounds" for clinical pharmacologists would appear extremely shortsighted. Such a rigid policy not only takes much of the excitement out of research, but is contrary to the time-proved principle that investigation must pursue promising leads whenever and wherever they occur. Three recent examples of such research in our division may be cited as illustrations of this point.[2-4]

The amount of time available to train a clinical pharmacologist must be somewhat flexible, although at present it is our opinion that two years would be adequate. It is envisioned that the program set up at our institution will serve as a "seeding" operation, with men being trained here and then going on to other institutions, there to train still other investigators. Our first fellow, Dr. William P. McCann, is now in the Department of Pharmacology at the University of Colorado. Obviously, the starting of such programs at other institutions will serve to accelerate this program. Ultimately, it is hoped that a "snowballing" phenomenon will provide enough investigators to meet the needs both of the universities and of the drug industry.

An interesting result of the program thus far has been the considerable interest shown in it by other universities. During the last year representatives of four university hospitals have consulted with us in the hope of developing programs of their own. In three instances, the men who would be in charge of these programs have inspected our program at first hand. We hope to continue this function, believing that a few days or weeks spent observing one such program in action (perhaps with repeat visits at later intervals) can serve as a useful compromise in the initiation of other programs until the supply of fully trained clinical pharmacologists becomes adequate.

Recently there has been a most encouraging development—the establishment of training grant programs in clinical pharmacology by the National Heart Institute. Several such long-term grants have been activated as of July 1959, with sufficient funds to permit each institution to support a number of trainees at any given time. (In our own group, this has meant an expansion from one to four fellows.) Support at this level, which is unlikely to derive from sources outside of the government, should greatly speed the growth of first-rate pharmacologic research in man.

## REFERENCES


1. Williams, R. H.: Departments of medicine in 1970. I. Staff policies. Ann. Int. Med. 50:1252, 1959.
2. Lasagna, L. and McCann, W. P.: Effect of "tranquilizing" drugs on amphetamine toxicity in aggregated mice. Science 125:1241, 1957.
3. McCann, W. P. and Jude, J. R.: The synthesis of glucose by the kidney. Bull. Johns Hopkins Hosp. 103:77, 1958.
4. Zikria, B. A., Lasagna, L. and McCann, W. P.: The relative importance of blood and urinary concentrations of sulfonamide in the treatment of urinary tract infections. Bull. Johns Hopkins Hosp. 103:117, 1958.

# Self-help Devices:
## Garment Fastener

EDWARD W. LOWMAN AND HOWARD A. RUSK

Institute of Physical Medicine and Rehabilitation
and the Arthritis Self-help Device Office*

*New York University-Bellevue Medical Center, New York*

AMONG the Functional Fashions illustrated in last month's article were several garments having VELCRO® closures, a new fastener which requires a minimum of finger dexterity to open and close. A large selection of ready-to-wear apparel with this type of closure is now available.

While it has been impossible for us to test the functioning and durability of the Velcro closure in all of the garments illustrated or listed, our selection has been guided by research done by Lubar Associates, 6 East 39th Street, New York, and a reliable consumer's report, which states ". . . tests confirmed that the grip of the Velcro closure was quite adequate for ordinary purposes . . . during dry cleaning and laundering tests, color fastness was also checked and no bleeding or loss of color was found . . . (Velcro should not be ironed directly with a hot iron—over 375° F.)."

A complete list of available garments and commercial sources may be obtained from the Arthritis Self-help Device Office, Institute of Physical Medicine and Rehabilitation, 400 East 34th Street, New York 16.

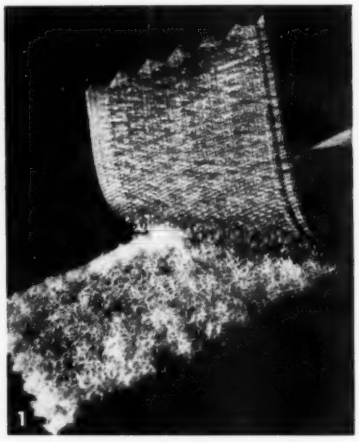


FIGURE 1. The Velcro closure consists of two strips of DU PONT® nylon tape. One strip is covered with a myriad of closely packed filaments tipped with minute permanent hooks; the other strip is covered with tiny, soft multifilament yarn. When the tapes are lightly pressed together, the hooks and loops engage, creating a highly adjustable and secure closure.

*Supported at the Institute by the Arthritis and Rheumatism Foundation.

FIGURE 2. Both the jacket for young boys *(left)* and the one for older boys *(right)* are interlined and well made. Chief Apparel, 10 West 33rd Street, New York. $12.95 and $19.95, respectively.

FIGURE 3. Fine finger movement is eliminated completely in fastening this brassière, designed by Charm Fit for Sears, Roebuck and Co. About $5.00.

FIGURE 4. Lady Berkleigh pajamas have the Velcro closure in both the shirt and pants. Columbia Shirt Company, 180 Madison Avenue, New York. $4.95 to $5.95.

FIGURE 5. The Ro Jene wrap-around half slip fits smoothly and eliminates over-the-head and step-into dressing. Roth Silk Undergarment Company, 102 Madison Avenue, New York. $3.95 to $5.00.

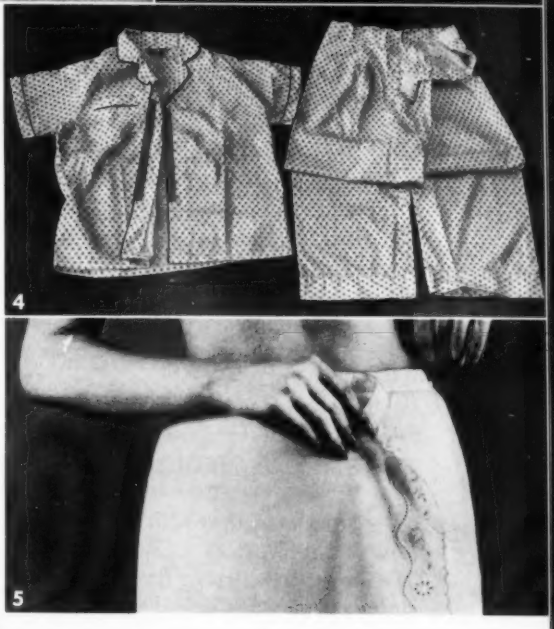


FIGURE 6. The Velcro closure on each side of this wool skirt provides a wider girth for over-the-head or step-into dressing and a waistline adjustment of several inches. Ann Marie Sportswear, 1372 Broadway, New York. $5.00 to $10.00.

FIGURE 7. This blouse in silk or jersey also features the wrap-around style, which adjusts to various waist sizes. It comes in black, navy or red polka dots on white background and in solid colors. Irene Originals, 525 Seventh Avenue, New York. About $11.00.

Readers are invited to submit suggestions and ideas for devices they have developed or know about and would like to share with others. Forward all such suggestions and comments to: Editorial Department, POSTGRADUATE MEDICINE, Essex Building, Minneapolis 3, Minnesota.

Additional information on self-help devices, aids for disabled persons, homemaking training, and other principles of physical medicine and rehabilitation will be found in the new book, "Arthritis," edited by Dr. Lowman and published by Little, Brown & Company, Boston, Massachusetts.

# Editorials

Postgraduate Medicine

*Editor-in-Chief:*
CHARLES W. MAYO, M.D.

*Contributing Editor:*
MORRIS FISHBEIN, M.D.

*Executive Editor:*
SYLVIA COVET

## GENETICS IN MEDICAL RESEARCH

A STRIKING feature of a recent issue of the *Journal of Medical Education*[1] was a symposium on genetics in medical research. The development of medical genetics has been much slower than has that of genetics related to animals and plants. A survey taken in 1953 indicated that only six medical schools offered formal courses in this subject. Obviously, research on human genetics cannot follow the same procedures used in the work with plants and animals, including insects.

In his opening address, Dr. James V. Neel, department of human genetics, University of Michigan Medical School, called attention to two recent examples which illustrate how one can analyze in man the dynamics of the difference in fertility between two genotypes. For instance, people afflicted with neurofibromatosis, which is a dominantly inherited trait, have a reproductive expectancy at birth which is 52.7 per cent of that of their normal siblings. In a series of 223 patients with this disease, 19 had fatal or incapacitating involvement of the brain or spinal cord prior to age 30. A diminished life span is therefore a factor in the reduced reproductive expectancy. A second example relates to Huntington's chorea, which is a dominantly inherited trait. A study was made of all the families in Michigan in which this disease has ever been recorded. A significant difference in fertility was observed between men and women. As in the case of neurofibromatosis, this difference may be due to both a lower marriage rate of the men and a lower rate of reproduction after marriage.

Studies of genetics are significant in the investigation of the genetic structure of various populations. Most exciting are the discoveries in the field of human biochemical genetics. For instance, certain quinine derivatives brought about hemolytic reactions in some persons because of a loss of activity in the erythrocytes of the enzyme glucose-6-phosphate dehydrogenase. This appears to be an inherited trait which is due to a sex-linked gene of intermediate dominance. Sensitivity to ingestion of the fava bean, which results in severe hemolytic anemia, and hemolytic reactions following the administration of sulfonamides, acetanilid or nitrofurantoin or the accidental ingestion of

naphthalene also may be due to deficiency of the same enzyme.

Dr. Curt Stern, department of zoology, University of California, discussed the "Chromosomes of man," recognizing the great debate which concerns the finding of an extra chromosome on occasion. Dr. Arthur G. Steinberg, Western Reserve University, discussed "Methodology in human genetics" and the technics used in these studies, which, incidentally, require a considerable knowledge of mathematics.

A brilliant address was given by Hilary Koprowski, Wistar Institute of Anatomy and Biology in Philadelphia, who considered the "Importance of genetics of viruses in medical research." This learned discussion was filled with both humorous and philosophical references, beginning with the story of the general who was asked how our modern weapons compared with those of the Russians. He replied, "We must catch up with them, but of course we are ahead of them." This is analogous to the position of mammalian viruses as opposed to the genetics of bacteriophages. Pasteur was the first to attempt to manipulate a virus to obtain variation of its character. He did this with the rabies virus when passing it through rabbits. Most physicians are aware of the work of Koprowski in obtaining mutations of the poliovirus. Many viruses have host specificity, for example, those of rabies and influenza, the adenovirus, and the virus of leukemia of the mouth. Referring to the difficulties of classification, Dr. Koprowski quoted the following story told by Robert Graves. An old lady traveling by train from London to Edinburgh was taking a pet tortoise in a basket and wanted to know whether she should buy a dog ticket for it, as one is required to do in England for cats because cats officially count as dogs. "No," said the ticket inspector, "no, mum. Cats is dogs, and rabbits is dogs, and dogs is dogs, and squirrels in cages is parrots, but this here turtle is a hinsect. We won't charge you nothing, mum!"

Dr. Ray D. Owen, biology division, Oak Ridge National Laboratory, Oak Ridge, Tennessee, began a discussion of "Genetic aspects of tissue transplantation and tolerance" by calling attention to the diversity among the individual species when considering tissue transplantation. "Surgeons today consider it axiomatic that a skin graft from one person will be rejected by any other person, unless the donor and recipient are identical twins. . . . The fact that identical twins constitute the universally recognized exception to the incompatibility of tissue transplants between individuals reflects the recognition that this kind of variation is inherited."

Dr. John B. Graham, department of pathology, University of North Carolina, spoke on "The inheritance of 'vascular hemophilia': A new and interesting problem in human genetics." The hereditary character of this condition has received tremendous study; however, the crucial experiments remain to be done. It has been suggested that other obscure hemorrhagic disorders may represent double heterozygosity for mild defects and that genetic analysis of the families of such patients is important.

An extensive series of papers concerned the knowledge of heredity that has been developed through studies of blood groups and relationships such as that of the ABO blood groups to ulcer, cancer and other diseases.

Among the fields of study at present dominating the scene in medical genetics are the genetic implications in the causation and prevention of congenital malformations, metabolic diseases and degenerative phenomena. This symposium on genetics in medical research was initiated by conversations between representatives of the National Institutes of Health and of the University of Wisconsin. Each medical school was invited to send a teacher concerned with the development of medical genetics in his own institution. The Association of American Medical Colleges is to be highly commended for its foresight and vision in planning the symposium. Dr. John Z. Bowers, editor in chief of the *Journal of Medical Education*, was chairman of the planning committee.

MORRIS FISHBEIN

REFERENCE

1. A symposium on genetics research. J. M. Educ. 34: 290-423 (April) 1959.

## SPECIALISM IN MEDICINE

THE first specialty board, that for ophthalmology, was organized in 1917. Conditions before that time were chaotic, if not menacing. The usefulness of the specialty board was so clearly apparent that by the early 1930s 13 new specialty boards had been established, and the members of the American Medical Association saw the need for some standardization and coordination in this area.

In February 1959, under the auspices of the Council on Medical Education and Hospitals of the American Medical Association and the Advisory Board for Medical Specialties, a conference on specialism in medicine was held in Chicago. Dr. Leland S. McKittrick, chairman of the Council, noted that a primary problem at this time is the development of subboards, particularly in the fields of surgery and internal medicine. He asked, "Is it easier to make a good specialist out of a well-trained surgeon or a good surgeon out of a well-trained specialist?"

By 1958 the 18 specialty boards represented on the Advisory Board for Medical Specialties had examined candidates and issued certificates in 51 different specialties or subspecialties of medicine. As pointed out by Dr. Ernest L. Stebbins, the reasons for this trend toward specialism are many; particularly apparent is the fact that rapid technologic changes are occurring in our civilization, and special training may be necessary both to understand and to use the new devices which are being developed. Dr. Paul M. Gross, vice-president of Duke University, called attention to the bewildering complexity of our social structure with its profusion of implements, machines, instruments, devices, gadgets and specialism. Dr. Gross observed that a better understanding of nature is immensely complex and involved and that problems can be answered only by concentrated, competent and enlightened attack on numerous limited areas. He did not, however, indicate the importance of generalizers capable of synthesizing available knowledge and of solving problems through such synthesis.

Dr. Moody E. Prior, dean of Northwestern University Graduate School, noted that the public and the professions admire specialists, and the generalists are out of fashion if not out of date. Recognition of the general practitioner when he is near the close of an honorable career is something sentimental and nostalgic. Dr. Prior is encouraged by the current preoccupation with the need for broadness in education and with the increasing criticism of naturalness and overspecialization. Nevertheless, our civilization depends on specialists, and the advancement of learning requires specialization.

Dr. Iago Galdston stated that the technics of medicine have tended to overshadow and outstrip the knowledge and understanding of man as a living creature, but that the time is near when less emphasis is likely to be placed on the technic. He believes that we are now on the verge of a situation in which the emergent unifying principles of the biologic sciences, reflected notably in the disciplines of physiology and ecology, will make of medicine a consistent and meaningful discipline.

Following the conference was a workshop at which various authorities discussed the phases of education for specialization, from training in the basic sciences through the clinical aspects of medical care, the work of the intern, the resident and the assistant.

While no specific recommendations were made, the conference was thought-provoking and indicative of the great gains to be achieved when groups of leaders can assemble to express their points of view based on experience and when a free interchange of knowledge and opinion is made possible.

MORRIS FISHBEIN

## BCG—PRO AND CON

IF it were fully established that vaccination with BCG would prevent tuberculosis in a person exposed to that disease, no one would question its widespread use. Nevertheless, as was pointed out in the *British Medical Journal*,[1] a test comparable to those used to determine the existence of immunity to diphtheria, tetanus, pertussis or poliomyelitis is not available. Undoubtedly, satisfactory vaccination

with BCG results in tuberculin allergy; however, the significance of this phenomenon is not quite clear. These editorial statements appeared in the same issue of the *British Medical Journal* in which a paper entitled "The case against B.C.G."[2] was published. This paper was written by some 17 authors, including members of the staffs of medical schools, directors of tuberculosis sanatoriums, leaders in the field of public health, and such distinguished authorities as J. A. Myers, E. A. Meyerding, George C. Ornstein and E. R. Levine. This combined statement is most impressive and will have a powerful effect in bringing forward proponents and opponents to the use of BCG in programs for the eradication of tuberculosis.

Among some of the most significant points emphasized in the summary of the afore-mentioned article were the following:

"Allergy to tuberculoprotein is not an indication of immunity, but is prerequisite to the development of clinical tuberculosis.

"An adequately controlled study of B.C.G. among people living in their homes has never been accomplished. It has been found impossible to do.

"Among people, the most phenomenal accomplishments in tuberculosis eradication have been achieved where little or no B.C.G. has been used, including Iceland, Hawaii and the Netherlands.

"The numerous values of the tuberculin test in diagnosis, epidemiology, etc., are lost to persons whose tissues have been sensitized to tuberculoprotein by B.C.G."

In the same issue of the *British Medical Journal,* there appeared a report by Lorber and Menneer[3] from the University of Sheffield. In their research, 267 children, aged two years or less, who were in close household contact with cases of tuberculosis remained tuberculin-negative six weeks after segregation from contact. All of the children were vaccinated with BCG between October 1949 and October 1952, and 261 were traced for five years or more after vaccination. There were no deaths from tuberculosis; two of the children had minor clinical symptoms associated with tuberculous lung lesions which healed by calcification, and one had a calcified lung lesion. In contrast, 39 patients who were classified as "index cases" died of tuberculosis, and 28 still had active disease. The authors conclude, "As there were no comparable controls it cannot be shown conclusively that B.C.G. vaccination prevented tuberculosis in this group of infants. Nevertheless the results are highly suggestive that this, in fact, was the case." It was pointed out in an editorial comment that the consistent achievement of highly suggestive results has encouraged advocates of BCG vaccination to continue their work.

Under the auspices of the World Health Organization, millions of children throughout the world have been vaccinated with BCG. However, these results do not constitute in any sense of the word a conclusive investigation. Here is a problem for which an answer still remains to be found.

The important fact is that a group of antagonists to BCG vaccination, whose names command great respect in the field of tuberculosis, have joined to express their doubts and that a leading medical publication has offered their views to the medical world.

MORRIS FISHBEIN


REFERENCES

1. EDITORIAL: For and against B.C.G. Brit. M. J. 1: 1458-1459 (June 6) 1959.
2. ANDERSON, A. S. ET AL.: The case against B.C.G. *Ibid.*, pp. 1423-1430.
3. LORBER, J. and MENNEER, P. C.: Long-term effectiveness of B.C.G. vaccination of infants in close contact with infectious tuberculosis. *Ibid.*, pp. 1430-1433.


## THE BRAIN OF THE ELEPHANT

POPULAR beliefs assert that an elephant never forgets. Many other characteristics of the actions of elephants have caused special interest in determining how the brain of the elephant may differ from that of the human being or other animals.

In several foreign institutes which have cooperated in this project, the brains of four elephants—two adult and two which were one month of age—were intensively studied.[1] The investigators found that the basal regions of

the frontal and temporal lobes especially are highly developed, whereas the entire neopallium is relatively large in comparison with that of other large mammals, including the anthropoid apes. The gyri of the cortex resemble those of the apes, and the pons and the cerebellum also are large. The cerebellum, relative to the cerebrum, is larger than in any other mammal. The temporal lobes expand greatly to the sides. The gyrus olfactorius shows a number of fissures and convolutions. The large size of the paleocortex seems referable to the excellent olfactory sense as well as to the oral sense of the elephant. The investigators believe also that the large temporal lobes are related to the good hearing sense of the elephant and to its ability to learn through hearing. The absence of distinct occipital lobes is related to the poor vision of the elephant.

MORRIS FISHBEIN


REFERENCE

1. Janssen, P., Stephan, H., Diepen, R., Engelhardt, F. and Spatz, H.: The brain of the African elephant (*Loxodonta africana Blum*). Acta neurol. et psychiat. belg. 56:731-812, 1959.


## A NEW POPULATION TENDENCY

According to statistics of the Metropolitan Life Insurance Company,[1] a definite tendency has developed in recent years for women in the United States to marry earlier and to have larger families. The trend has been stimulated by the improved economic conditions since World War II. In 1958, there were 41.5 million married women in the country, a gain of approximately 11.33 million since 1940. About 72 per cent of women in the United States more than 18 years of age are married. The number was 65 per cent in 1940. Over the same period, the birth rate has risen substantially from 125.9 per 1000 married women at ages 15 to 44 in 1940 to about 159 in 1956. The birth rate for wives in the age group 20 to 30 increased more than a third, and the rate among women of 30 to 40 increased about a fourth. This has definitely influenced the maternal death rate, because the hazards of maternity are lowest among younger women. Today seven of every 10 babies are born to mothers who are less than 30 years of age, and one-eighth of the mothers are less than 20 years of age.

These trends are reflected in the incidence of larger families. Third, fourth and fifth births constituted 37 per cent of all births in 1956, a gain of 10 per cent over those in 1940. Maternal mortality is now about four deaths of mothers for every 10,000 live births. The rate in 1940 was 38 for every 10,000 births. At this time, 95 per cent of all births in the United States are in hospitals; in 1940, the number was only 55 per cent.

A further indication of the changing status of women is the fact that one-third of all the married women in the United States are now included in the labor force. Most of these are women in the age group 45 to 54. In this group, nearly two of every five wives are working. The tendency is for women to seek employment after their children have grown. The records indicate that six million women who work still have children less than 18 years of age in their care and 2.4 million have children less than six years of age in their household. The experts in the social sciences have taken these figures as suggesting that conceivably the absence of the mother from the home may bear some relationship to problems of social adjustment, including juvenile delinquency.

MORRIS FISHBEIN


REFERENCE

1. American Wives and Mothers. Statistical Bulletin issued by Metropolitan Life Insurance Company, New York, June 1959.

# PARTICULARLY for the "OB" patient who requires antibiotic therapy

## COSA-TETRASTATIN®

*glucosamine-potentiated tetracycline with nystatin*

Because women during pregnancy are particularly prone to secondary fungal infection, they benefit from the extra protection of nystatin.

*Cosa-Tetracyn*® (glucosamine-potentiated tetracycline) provides peak levels of antibiotic activity against a broad range of susceptible organisms.

*Nystatin* provides specific protection against overgrowth of Candida albicans.

COSA-TETRASTATIN *provides tetracycline effectiveness with minimum risk of moniliasis.*

***Supplied:***

**Capsules**
***(pink & black)***
250 mg. Cosa-Tetracyn plus 250,000 u. nystatin

**Oral Suspension**
***(orange-pineapple flavor)***
2 oz. bottle, each tsp. (5 cc.) contains 125 mg. Cosa-Tetracyn plus 125,000 u. nystatin

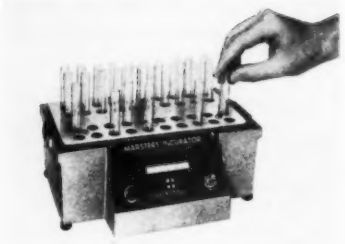
***A Professional Information Booklet providing complete details on Cosa-Tetrastatin is available on request.***

*Pfizer Science for the world's well-being™*

PFIZER LABORATORIES
*Division, Chas. Pfizer & Co., Inc.*
*Brooklyn 6, N. Y.*

# New *for your armamentarium*

*Information published in this department is supplied by the manufacturers of the products described.*



**• MARSTERS TEST TUBE INCUBATOR**

DESCRIPTION: For use in blood banks and hematology laboratories, this unit features waterless operation and provides accurate temperature control at 37° C., ± 0.5 degree, for up to 40 test tubes at one time. Up to 2 ml. fluid may be incubated in each tube. Operating temperature is reached in 30 minutes, and specimens reach 37° C. within four or five minutes. The incubator measures 9½ by 7 by 3 in., weighs 9 lb., and operates on a 110 to 115 V, 50 to 60 cycle AC circuit. It is of aluminum block construction, finished in gray hammertone enamel with a chrome steel top plate.
PRODUCER: Clay-Adams, Inc., New York.

**• ACHROSURGIC® TOPICAL SPRAY POWDER**

PURPOSE: Antibiotic.
COMPOSITION: ACHROMYCIN® tetracycline.
HOW SUPPLIED: In aerosol cans.
PRODUCER: American Cyanamid Company, Surgical Products Division, New York.

**• NITRETAMIN-10**

PURPOSE: Coronary vasodilator.
COMPOSITION: Each tablet contains 10 mg. triethanolamine trinitrate diphosphate.
CAUTION: Mild side effects, such as headache, gastric upset and dizziness, may occur infrequently.
DOSAGE AND ADMINISTRATION: 1 tablet twice daily.
HOW SUPPLIED: Bottles of 50; also available in 2 mg. tablets in bottles of 50.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corporation, New York.

**• EMPRAZIL®**

PURPOSE: Symptomatic relief of common cold and influenza.
COMPOSITION: Each tablet contains:

| | |
|---|---|
| SUDAFED® (pseudoephedrine hydrochloride) | 20 mg. |
| PERAZIL® (chlorcyclizine hydrochloride) | 15 mg. |
| Acetophenetidin | 150 mg. |
| Aspirin | 200 mg. |
| Caffeine | 30 mg. |

CAUTION: Administer with care in cases of hypertension. May cause drowsiness.
DOSAGE AND ADMINISTRATION: Adults and older children, 1 or 2 tablets three times a day; children 6 to 12 years of age, 1 tablet three times a day.
HOW SUPPLIED: Bottles of 100 and 1000.
PRODUCER: Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, N. Y.

*(Continued on page A-160)*

completes the picture in high starch diets

# TAKA-COMBEX®

## KAPSEALS®

to help digest carbohydrates • to forestall vitamin deficiencies

*Each Kapseal contains:*

Taka-Diastase® (aspergillus oryzae enzymes) 2½ gr.
Vitamin $B_1$ (thiamine) mononitrate ..... 10 mg.
Vitamin $B_2$ (riboflavin) ..... 10 mg.
Vitamin $B_6$ (pyridoxine hydrochloride) .... 0.5 mg.
Pantothenic acid (as the sodium salt) ..... 3 mg.
Nicotinamide (niacinamide) ..... 10 mg.
Vitamin C (ascorbic acid) ..... 30 mg.
Vitamin $B_{12}$ (crystalline) ..... 1 mcg.
Liver Concentrate, N. F. ..... 0.17 Gm.
Liver Fraction No. 2, N. F. ..... 0.17 Gm.

Supplied in bottles of 100 and 1,000.

TAKA-COMBEX elixir containing Taka-Diastase, Vitamins $B_1$, $B_2$, $B_6$, pantothenic acid, and nicotinamide is also available in 1-pint bottles.

*Other dependable* COMBEX *products:*
when requirements for B-complex are increased

**COMBEX® KAPSEALS**
bottles of 100, 500, and 1,000

for combined B-complex and C deficiencies

**COMBEX WITH VITAMIN C KAPSEALS**
bottles of 100, 500, and 1,000

for a rapid increase in B-complex reserves

**COMBEX PARENTERAL**
10-cc. Steri-Vials®

for correction of severe vitamin B-complex and C deficiencies

**THERA-COMBEX® KAPSEALS**
bottles of 100 and 1,000

**PARKE, DAVIS & COMPANY**
**DETROIT 32, MICHIGAN**

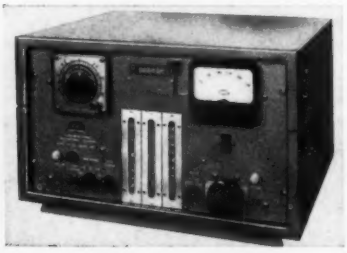
92659

**• HUMORSOL**

PURPOSE: To treat glaucoma.
COMPOSITION: 0.25 per cent aqueous solution of demecarium bromide.
CAUTION: Not indicated in the presence of active uveal inflammation.
DOSAGE AND ADMINISTRATION: Topically.
HOW SUPPLIED: 5 cc. dropper vials.
PRODUCER: Merck Sharp & Dohme, division of Merck & Co., Inc., Philadelphia.

**• ZOLYSE®**

PURPOSE: For use in cataract surgery.
COMPOSITION: Alpha-chymotrypsin.
DESCRIPTION: Zolyse contains a proteolytic enzyme which specifically dissolves the zonules (fibrils that hold the lens in place) so that the lens may be removed more easily with less damage to other ocular tissue.
HOW SUPPLIED: Packages containing one vial of 750 units alpha-chymotrypsin and one 10 cc. vial of balanced salt solution for use as the diluent and lavage.
PRODUCER: Alcon Laboratories, Inc., Fort Worth.



**• PC-3A PROPORTIONAL COUNTING SYSTEM**

DESCRIPTION: Designed for precision counting of $H^3$, $C^{14}$, $Ca^{45}$ and $S^{32}$, the instrument counts beta radiation in the presence of alpha without absorbers, and alpha in the presence of beta. The unit can be used as a scaler independently of the proportional counting chamber, and can power and count from gamma scintillation, beta-gamma GM, and flow-type GM counters. The system consists of counting chamber, transistorized amplifier-discriminator, magnetostatically regulated high-voltage supply and precision timer.
PRODUCER: Nuclear Measurements Corporation, Indianapolis.

**• BIOLOGICAL SAFETY CABINET**

DESCRIPTION: Suitable for use in the study and safe handling of all disease-causing microorganisms, this unit provides stations for two technicians. A slight negative pressure inside the cabinet insures inward movement of air, thus protecting the operator from infectious aerosols and outward diffusion of particles. Filtration and ultraviolet radiation clean the exhaust air. The filters have a minimal tested efficiency of 99.97 per cent for particles 0.3 $\mu$ in diameter; efficiency increases as particles collect on the filter media.

The cabinet is constructed of heat-resistant and reagent-resistant material finished in smooth, nonporous dull black lacquer. It is mounted on a wooden base and measures 72½ by 84⅜ by 30½ in. A 12 by 6 in. stainless steel sink with self-closing faucets for cold water and formaldehyde is located at the left end of the cabinet; ground key cocks for gas, air and vacuum are located at both ends.

Accessories include a manometer assembly, which measures air pressure and filter operation; germicidal light indicators; an external fluorescent light; and a PYREX® trap.
PRODUCER: Hamilton Manufacturing Co., Two Rivers, Wis.

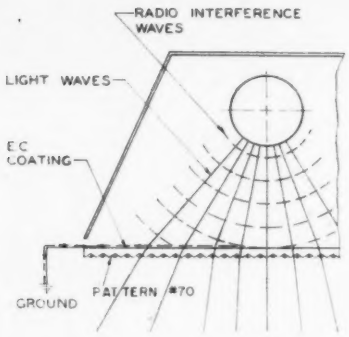
**• STILLE NEEDLE HOLDERS**

DESCRIPTION: To enable the user to maintain a firm grasp, these needle holders have straight single-cut serrations in one jaw and double cross-cut serrations in the other. New models available are the 8 in. Bjork, the 7½ in. Potts and the 7 in. New Orleans.
PRODUCER: Ohio Chemical & Surgical Equipment Co. (A division of Air Reduction Company, Inc.), Madison, Wis.

*(Continued on page A-162)*

your ambulant asthmatic . . . **"Air in a hurry!"**

**phenalin®**, the square purple tablet that relieves asthma with nebulizer speed for 4 full rs, offers convenience and reassurance to your ambulant asthmatic patient. Placed under the ue, the NEPHENALIN tablet quickly releases 10 mg. of Isoproterenol HCl, the potent homo- e of epinephrine, for immediate opening of the airway. Swallowed, the NEPHENALIN tablet ides theophylline (2 gr.), ephedrine (3/8 gr.) and phenobarbital (1/8 gr.), for sustained ection from asthmatic seizure. NEPHENALIN is available for your prescription in bottles of nd 100 tablets. Also available: NEPHENALIN PEDIATRIC. *Thos. Leeming & Co. Inc.* NEW YORK 17, N.Y.




**• LOW-BRIGHTNESS LENS PANEL (Model EC No. 70)**

DESCRIPTION: Developed for areas in which sensitive equipment is used, this lighting panel eliminates radio interference radiated from fluorescent lamps while transmitting light waves. A thin, transparent electrically conductive film on the back surface of the glass intercepts the interference, which then is grounded by a ¼ in. silver strip fired onto the film around the periphery of the glass. Made of heat-resistant borosilicate glass, the panel resists heat shock and corrosion. Its prismatic design assures accurate control of direct and reflected light. The panel weighs 1.8 lb. per square foot; it is approximately ⅛ in. thick, and can be cut to any size up to 28 in. wide and 48 in. long.
PRODUCER: Corning Glass Works, Corning, N.Y.

**• SLIDE-SORTER**

IMPROVED MODEL: Improved lighting and light ray diffusion have been combined to make this unit more effective for sorting photographic slides. This improvement has been achieved by use of a blue lighting unit which transmits white light through a light-diffusing translucent top.
PRODUCER: The H. E. Geist Company, Cleveland.

**• MADRIBON®**

NEW PRODUCT FORM: This long-acting, low-dosage antibacterial is now available in palatable drop-dosage form for infants and young children.
HOW SUPPLIED: 10 cc. plastic containers with dispenser tops.
PRODUCER: Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, N. J.

**• ELIXIR NOLAMINE**

PURPOSE: To relieve nasal congestion.
COMPOSITION: Each teaspoonful (5 cc.) contains:

| | |
|---|---|
| Chlorprophenpyridamine maleate | 1 mg. |
| Phenindamine tartrate | 6 mg. |
| Phenylpropanolamine hydrochloride | 12.5 mg. |
| D-sorbitol | 1 gm. |

CAUTION: Should be used with caution in hyperthyroid and hypertensive patients and those sensitive to antihistamines.
DOSAGE AND ADMINISTRATION: For adults, 2 teaspoonfuls every three or four hours; for children aged six and older, 1 teaspoonful every three or four hours; for children aged one to six, ¼ to 1 teaspoonful every four hours according to age and weight.
HOW SUPPLIED: 16 oz. bottles.
PRODUCER: G. W. Carnrick Company, Newark, N. J.

**• 399AV FILMOSOUND® SPECIALIST**

DESCRIPTION: Developed exclusively for audiovisual application, this 16 mm. motion-picture projector features a self-contained, two speaker panharmonic sound system. An interlocked clutch and a heat filter permit the projector to stop at any point, projecting a still picture without damage to the film. An automatic loop restorer resets a lost loop of film without loss of picture. Equipped with a 2 in. f/1.6 Super Proval lens, the projector is also available with the Bell & Howell Filmovara zoom projection lens. It operates on a 90 to 130 V, 15 W, 60 cycle AC-DC circuit. The unit is enclosed in a laminated plywood case of a metallic fawn color with dark brown trim. A tri-fi speaker in a matching case is available for use in large halls or auditoriums.
PRODUCER: Bell & Howell Company, Chicago.

*(Continued on page A-164)*

# dust
## a major offender

Dust is a principal offender in allergies of the respiratory tract. It cannot be avoided — and the dust-allergic patient requires medical attention. POLARAMINE — the closest to a perfect antihistamine — is the closest to a perfect solution for the problem of the patient suffering from irritating nonseasonal allergens. POLARAMINE offers swift, sure, safe action with these outstanding advantages — • Therapeutically effective at lower dosages than other antihistamines • Highest therapeutic index of all antihistamines (3380) • Fewer side effects than with other antihistamine preparations • Highly efficacious — a single POLARAMINE REPETAB gives your patient all-day or all-night protection from discomfort of allergic symptoms

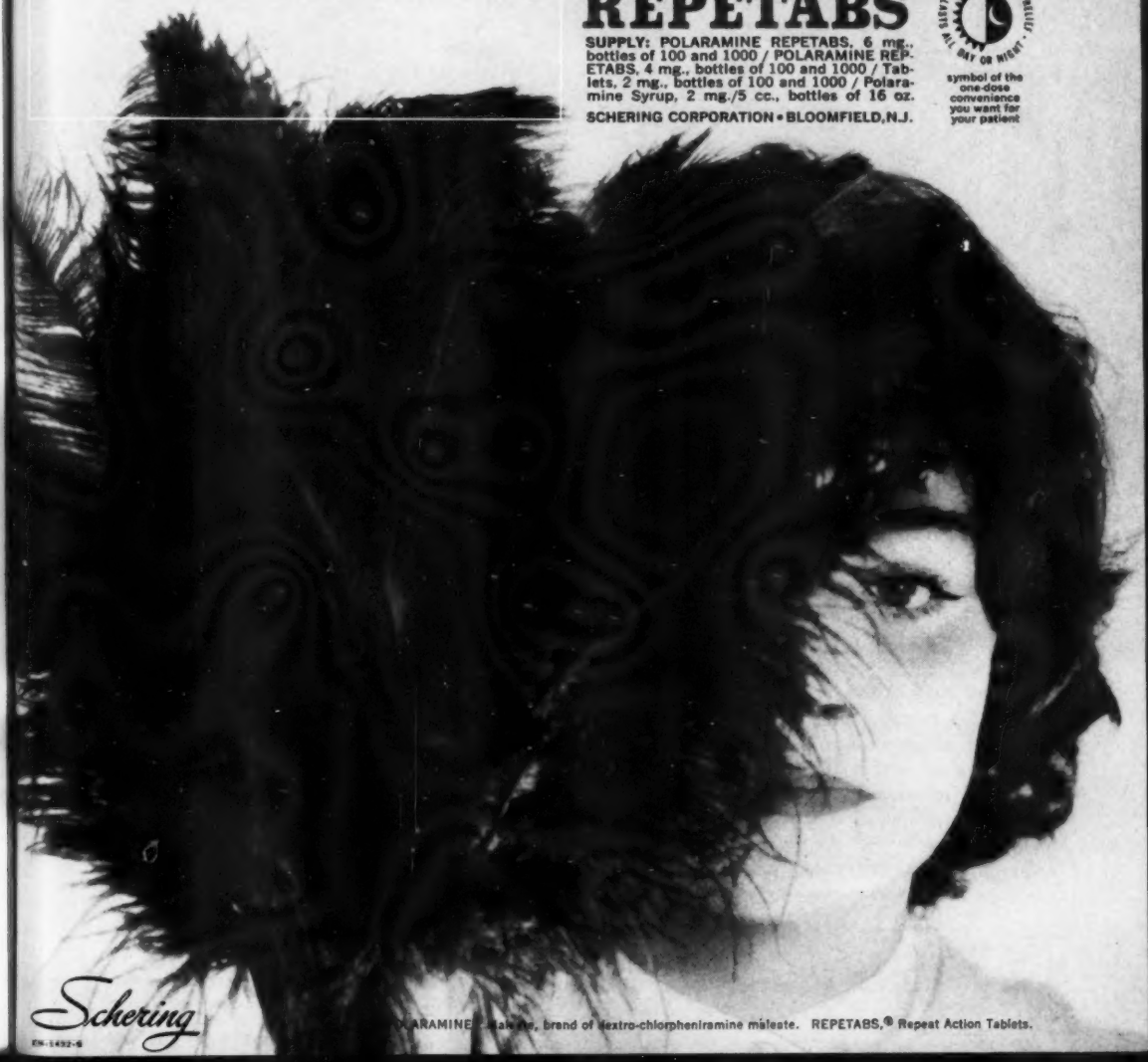
## POLARAMINE REPETABS

SUPPLY: POLARAMINE REPETABS, 6 mg., bottles of 100 and 1000 / POLARAMINE REPETABS, 4 mg., bottles of 100 and 1000 / Tablets, 2 mg., bottles of 100 and 1000 / Polaramine Syrup, 2 mg./5 cc., bottles of 16 oz.

SCHERING CORPORATION • BLOOMFIELD, N.J.

SAFE! • PROMPT REPETAB RELIEF! • ALL DAY OR NIGHT!

symbol of the one-dose convenience you want for your patient



Schering

EN-1432-S

...ARAMINE,® Make, brand of dextro-chlorpheniramine maleate. REPETABS,® Repeat Action Tablets.

### • CASAKOL CAPSULES AND SYRUP

PURPOSE: Fecal softener and mild laxative.
COMPOSITION: Each capsule or teaspoonful syrup contains 250 mg. poloxalkol (Polykol) and 30 mg. casanthranol.
CAUTION: If administered during pregnancy, the lowest effective daily dose should be used. In all cases, medication should be withdrawn after regularity is restored.
DOSAGE AND ADMINISTRATION: For children aged three to six, ½ to 1 teaspoonful syrup as needed; for children aged 6 to 12, 1 or 2 teaspoonfuls syrup or 1 or 2 capsules as needed. For adults, 2 or 3 teaspoonfuls syrup or 2 or 3 capsules until regularity returns, then 1 or 2 teaspoonfuls syrup or 1 or 2 capsules as needed. Medication should be given at bedtime.
HOW SUPPLIED: Capsules in bottles of 16 and 100; syrup in 4 fl. oz. and 1 pt. bottles.
PRODUCER: The Upjohn Company, Kalamazoo, Mich.

### • NORCOLD PIXIE REFRIGERATORS

DESCRIPTION: Designed to provide maximal cold storage in a small space, these completely noiseless electric refrigerators are available in 4 and 6 cu. ft. sizes. Both models have adjustable glide-out shelves, two ejector trays for ice cubes, a slide-out egg tray, a full-width crisper, and space for tall bottles; the larger model includes a zero-cold top freezing unit and an interior light. A special hinge design permits reversal of door opening to either side. The 6 cu. ft. model (596E) measures 45¾ by 25¾ by 27⅛ in.; the 4 cu. ft. model (594E) measures 34⅝ by 21¾ by 25⅛ in.
PRODUCER: NORCO, Incorporated, Los Angeles.

### • CERVICAL TRACTION HALTER

DESCRIPTION: Made of SANFORIZED® 12 oz. duck with a 12 oz. Canton flannel lining, this washable halter is adjustable and contoured for durability and comfort. Double stitching provides extra strength and retention of shape. The chin strap gives proper support, and adjustable side straps will not pinch the face. An Adjustable Spreader Bar securely holds the rings of the halter in any position. The halter is available in small, medium and large sizes.
PRODUCER: Rehabilitation Products, division of American Hospital Supply Corp., Evanston, Ill.

### • MYCOLOG® CREAM

NEW PRODUCT FORM: Mycolog dermatologic preparation is now available in vanishing cream formulation.
HOW SUPPLIED: 5 and 15 gm. tubes.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corporation, New York.

### • EFFERSYL

PURPOSE: To treat chronic constipation.
COMPOSITION: Each 7 gm. contains 3 gm. psyllium hydrocolloid and 3 mg. di(acetylhydroxyphenyl)isatin.
DOSAGE AND ADMINISTRATION: For adults, 1 rounded teaspoonful in glass of water morning and night; for children six years of age and older, 1 level teaspoonful in one-half glass of water on retiring. Subsequent dosage may be adjusted according to patient's needs. For children less than six years of age, as prescribed.
HOW SUPPLIED: 4 and 9 oz. bottles.
PRODUCER: The Stuart Company, Pasadena, Calif.

*(Continued on page A-166)*

When the emotional component of premenstrual tension becomes severe enough to interfere with normal activities and relationships, PROZINE is usually advantageous. It is designed for the treatment of moderate to severe emotional disturbances, either alone or complicated by organic symptoms.

PROZINE acts on both the thalamic and hypothalamic areas of the brain. As a result, PROZINE helps the physician control motor excitability as well as apprehension and agitation. This dual effect permits low dosages, which minimize side-effects and encourage the use of PROZINE in everyday practice.

*This time last month I would have screamed"*

# PROZINE*

meprobamate and promazine hydrochloride, Wyeth

SPECIFIC CONTROL THROUGH DUAL ACTION

Wyeth

Philadelphia 1, Pa

*Trademark

**• POWDETTE**

NEW PACKAGE FORM: This starch derivative powder, used to lubricate rubber gloves, is now available in 10 oz. shaker packages.
PRODUCER: Duxe Products, Cincinnati.

**• "BLUELINE" NO. 9 DRY HEAT STERILIZER**

DESCRIPTION: Designed to supplement the office autoclave, this FIBERGLAS®-insulated unit provides a safe, noncorrosive method of sterilizing fine cutting instruments, root-canal files and broaches, needles and glassware. The temperature range is from 300 to 375° F., with a temperature control of ± 6° F. Even-flow ventilation prevents heat stratification and provides for constant temperature within the chamber. A two hour automatic timer turns off the unit at the end of the sterilizing cycle. The sterilizer is 6¼ in. wide, 3¼ in. high, and 13¼ in. long.
PRODUCER: Wilmot Castle Co., Rochester, N.Y.

**• VANAY VAGINAL CREAM**

PURPOSE: Topical fungicide.
COMPOSITION: 250 mg. glyceryl triacetate per gram in a nonliquefying base.
INDICATIONS FOR USE: Moniliasis and nonspecific vaginitis in which an acid pH must be restored and maintained. Vanay may be used for adjunctive therapy in trichomoniasis, and it is especially indicated during pregnancy, in the presence of diabetes, and following use of antibiotics.
DOSAGE AND ADMINISTRATION: 2 to 4 gm. intravaginally at bedtime. During the acute stage of infection, medication should be administered in the morning and at night.
HOW SUPPLIED: 1½ oz. tube with 15 disposable applicators.
PRODUCER: Ayerst Laboratories, New York.

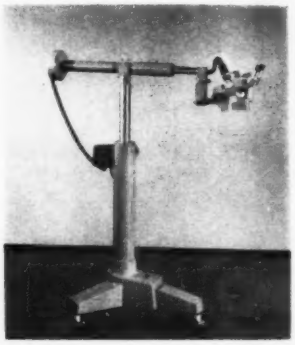
**• NITRAZINE® PAPER**

NEW PACKAGE FORM: Used for pH determination, Nitrazine Paper is now available as a 15 ft. ribbon roll in a plastic dispenser containing the color chart.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corporation, New York.

**• SALURON® TABLETS AND SYRUP**

PURPOSE: Diuretic.
COMPOSITION: Hydroflumethiazide.
HOW SUPPLIED: 50 mg. tablets in bottles of 50; syrup in 8 fl. oz. bottles.
PRODUCER: Bristol Laboratories, Inc., Syracuse.

**• SURGICAL MICROSCOPE**



DESCRIPTION: Providing three-dimensional magnification for surgical procedures and clinical examinations, this instrument also may be used as an otoscope. A Magni-Changer permits the user to dial the desired magnification. When the microscope is in focus, a distance of 8 in. exists between specimen area and objective. A wide range of adjustments permits the body of the microscope to be positioned quickly and easily over the exact area to be observed; all adjustments can be locked securely. The entire unit moves on locking ball-bearing casters.
PRODUCER: American Optical Company, Instrument Division, Buffalo.

**• SURFAK**

NEW PRODUCT NAME: This fecal softener formerly was called Doxical.
PRODUCER: Lloyd Brothers, Inc., Cincinnati.

■ Exhibits unusual analgesic properties, different from those of any other drug ■ Specific and superior in relief of SOMAtic pain ■ Modifies central perception of pain without abolishing natural defense reflexes ■ Relaxes abnormal tension of skeletal muscle

# SOMA™

N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate

■ More specific than salicylates ■ Less drastic than steroids

■ More effective than muscle relaxants

**SOMA** has an unique analgesic action. It apparently modifies central pain perception without abolishing peripheral pain reflexes. SOMA is particularly effective in relieving joint pain. Patients say that they feel better and sleep better with SOMA than with previously used analgesic, sedative or relaxant drugs.
SOMA also relaxes muscle hypertonia, with its stresses on related joints, ligaments and skeletal structures.

**ACTS FAST.** Pain-relieving and relaxant effects start in 30 minutes and last 6 hours.

**NOTABLY SAFE.** Toxicity of SOMA is extremely low. No effects on liver, endocrine system, blood pressure, blood picture or urine have been reported. Some patients may become sleepy, particularly on high dosage.

**EASY TO USE.** Usual adult dose is one 350 mg. tablet 3 times daily and at bedtime.

**SUPPLIED:** Bottles of 50 white coated 350 mg. tablets.

*Literature and samples on request.*

WALLACE LABORATORIES, NEW BRUNSWICK, N. J.

# THE MEDICAL *Bookman*

## ► ARTHRITIS
### General Principles, Physical Medicine, Rehabilitation

*Edited by Edward W. Lowman, M.D., Associate Professor of Physical Medicine and Rehabilitation, New York University College of Medicine, New York, with 24 contributors. 292 pages with 134 illustrations. 1959, Little, Brown & Company, Boston. $9.50.*

Past literary efforts in the field of arthritis and its related problems have been directed almost entirely to the clinical course of the rheumatic diseases, osteoarthritic changes and gout. It is, therefore, most refreshing and timely to review a monograph in which is recognized the magnitude of the over-all hardships facing the patient afflicted with a chronic disabling disease. The editor has gathered valuable information about numerous ancillary facets of treatment and has edited a volume that will appeal primarily to those especially interested in the disease, whether they are practitioners, laymen or patients.

The complexities of the predicament to which a patient or his family may have to adjust have engendered a hopeless attitude in many who have irreversible soft tissue damage associated with chronic disabling diseases. The editor of this book has endeavored to lighten this burden. He has succeeded adequately by presenting the subject matter clearly and in a language that can be understood readily. Chapters are devoted to the widely varied aspects of subjects such as shoe corrections, gait training, self-help devices, the role of the visiting nurse for the homebound arthritic patient, social problems, psychologic aspects, and job placements. Emphasis has been directed chiefly toward a general survey of the physical and social aids available to the patient; this material is presented in a manner which encourages active participation in community life in spite of physical handicaps.

The value of the book is enhanced by contributions from workers who specialize in one component of therapy. All fundamental forms of treatment are touched on, with pertinent endorsement by these authorities who have actively engaged in the care of such disorders.

E. H. O'P.

## ► MOLOY'S EVALUATION OF THE PELVIS IN OBSTETRICS

*By Charles M. Steer, M.D., Associate Professor of Clinical Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York. Ed. 2. 131 pages with 57 illustrations. 1959, W. B. Saunders Company, Philadelphia and London. $4.00.*

In this volume, which is profusely studded with graphic illustrations, the author describes pelvic architecture and guides the obstetrician in selecting methods of delivery. The significance of pelvic contractions and their effect on labor are clearly illustrated. The author also suggests the manner in which bony dystocia is best managed. The four fundamental types of pelves and their usual deviations are adequately described. The new section on roentgenographic mensuration is of value to the roentgenologist as well as to the obstetrician.

E. A. B.

*(Continued on page A-192)*

REFLECTION ON CORTICOTHERAPY:

Particularly in corticotherapy, the intent is not to treat diseases, but to treat patients. This intent is best served by using the steroid that has the best ratio of desired effects to undesired effects:

# Medrol*

the corticosteroid that hits the disease, but spares the patient

Upjohn THE UPJOHN COMPANY
KALAMAZOO, MICHIGAN

*TRADEMARK, REG. U. S. PAT. OFF. — METHYLPREDNISOLONE, UPJOHN

## ► PARSONS' DISEASES OF THE EYE

*By Sir Stewart Duke-Elder, M.D., Director of Research Institute of Ophthalmology, University of London, London, England. Ed. 13. 613 pages with 481 illustrations. 1959, The Macmillan Company, New York. $8.75.*

The first edition of this popular textbook appeared in 1907. Since the twelfth edition was published in 1954, the senior author has died, and the revision for the thirteenth edition was assumed by Sir Stewart Duke-Elder.

The present text incorporates new material (particularly in therapy), the importance of viral infections, and advances in our knowledge and understanding of the etiology and pathology of many ocular diseases. A rearrangement of some material has placed formerly disassociated subjects in sequence. The text is compact, comprehensive and adequately supplemented with 22 color plates and numerous other figures.

W. L. B.

## ► FUNDAMENTALS OF OTOLARYNGOLOGY

*By Lawrence R. Boies, M.D., Professor and Chairman, Department of Otolaryngology, University of Minnesota Medical School, Minneapolis, and seven associates. Ed. 3. 510 pages with 212 illustrations. 1959, W. B. Saunders Company, Philadelphia and London. $8.00.*

The basic premise of the first edition of this book, namely, to offer fundamental information to the student or physician who is not a specialist in otolaryngology, has been retained by the author. This new edition not only is authoritative, concise and well illustrated but also is up to date in every way and covers the majority of the phases of otolaryngology as practiced by specialists in large hospitals. The diagnostic and operative procedures and instrumentation are clearly shown in photographs and drawings. Anatomic, physiologic, pathologic and bacteriologic aspects are incorporated into each section. Step-by-step examination procedures are outlined and clearly explained.

Separate sections are devoted to the anatomy, physiology and examination of the ear, loss of hearing, various diseases of the ear, vertigo, and the science of audiology. The section on the nose is introduced by a description of nasal anatomy and physiology, followed by a discussion of the examination of the nose and a description of the problems of nasal obstruction, sinus disease, headaches of nasal origin, atrophic rhinitis, epistaxis, injuries, and reconstructive surgery. Similarly, the discussion on the throat covers all the afflictions of this area, with emphasis on diagnosis and treatment. Separate chapters are devoted to bronchoscopy, tumors of the nose and throat, disorders of the salivary glands, and medication in otolaryngology.

The general practitioner sees the majority of the patients with problems of the ear, nose and throat, and this textbook appears to cover adequately any problem which he is likely to encounter in this area.

Y. S.

## ► SYNOPSIS OF TREATMENT OF ANORECTAL DISEASES

*By Stuart T. Ross, M.D., Diplomate of the American Board of Proctology, Garden City, New York. 240 pages with 79 illustrations. 1959, The C. V. Mosby Company, St. Louis. $6.50.*

Rarely does one have the privilege of reading a medical text which does not wander from its primary aim. This circumambulation frequently adds to the readability and strengthens the thesis, but it always increases the reading time.

Dr. Ross has demonstrated his tenacity in adhering to his principal objective by writing a true synopsis containing most of the essentials of treating anorectal diseases. The reader is seldom aware of the extreme condensation of this book because it is adequately illustrated.

The discussion of treatment in a book of this type is characteristically limited, but the author wisely chose to present only the conservative surgical procedures. The reader should understand that other methods are equally acceptable.

The only deficiency that may limit the usefulness of this book is the lack of a discussion of diagnostic aids. In general, however, the text is worthy of recommendation to medical students, interns, residents and general practitioners. The necessary superficiality of a synopsis makes it of little use to surgeons or to one who is devoting his full interest to proctology.

R. J. S.

*(Continued on page A-194)*

# Counteract Depression with distinctively WELL-TOLERATED

# Deaner®

deanol acetamidobenzoate

- 'Deaner' may be prescribed with little or no concern over side effects even in the presence of liver disease, diabetes, cardiovascular disease, and a long list of other chronic conditions, except grand mal epilepsy (only contraindication).
- 'Deaner' *is not a monoamine oxidase inhibitor;* hence it is not necessary to monitor its administration with repeated, expensive laboratory tests.
- This notable freedom from side effects endows Deaner's long-term administration with easier patient supervision, better patient cooperation, and greater safety.
- Dosage is simple—initially, 50 mg. (2 tablets) daily in the morning. *Gradually, apathy and defeat are transformed into affability and renewed interest and vigor.*

Write for details and the applicability of 'Deaner' in behavior problems of children

Riker Northridge, California

## ► TRIGEMINAL NEURALGIA
### Its History and Treatment

*By Byron Stookey, M.D., Emeritus Professor of Clinical Neurological Surgery, and Joseph Ransohoff, M.D., Assistant Professor of Clinical Neurological Surgery, Columbia University College of Physicians and Surgeons, New York. 366 pages with 86 illustrations. 1959, Charles C Thomas, Springfield, Illinois. $10.75.*

For almost 200 years trigeminal neuralgia has been recognized as a unique but puzzling clinical entity. Attempts to explain its cause have been numerous, some ingenious, others fantastic, none valid. Proposed remedies for the condition are numbered in the hundreds, yet no truly satisfactory method of treatment is known. This book does not give final answers to the problems of etiology and treatment, but it is of value as a résumé of the extensive studies and experience of the authors. The facts and opinions they present deserve scrutiny by anyone interested in the condition.

The first chapter is of interest for its treatment of the history of the disease. The meager basis for claims that Aretaeus and Avicenna recognized trigeminal neuralgia is properly devaluated. Credit is given to the efforts of John Locke on behalf of the Countess of Northumberland who had the disease. The interesting correspondence between Locke and eminent physicians in England is reported in detail by Kenneth Dewhurst in "Symposium on trigeminal neuralgia," published in the January 1957 issue of the *Journal of the History of Medicine and Allied Sciences.*

Embryology, anatomy and physiology of the trigeminal and related cranial nerves are given thorough consideration. The detailed clinical description of trigeminal neuralgia and the differential diagnosis of various conditions causing pain which may resemble that of trigeminal neuralgia are appropriate to a book of this sort. However, from a practical standpoint, the pain of trigeminal neuralgia is so unique that differential diagnosis is rarely a problem. The discussion of atypical facial neuralgia is vague, a defect common to most discussions of this difficult subject. Nonsurgical treatment is dealt with briefly but with enough detail to justify the conclusion that no effective nonsurgical method of treatment has yet been advanced.

In the discussion of various surgical methods of treatment, the descriptions of surgical technic will interest neurosurgeons, while the rationale for the various procedures and results of each operation will interest all who deal with this disease. The historical background of trigeminal dorsal root section is presented and the authors are to be commended for stressing the fact that Sir Victor Horsley was the first to advocate and attempt division of the posterior root for relief of trigeminal neuralgia. The results of 728 posterior root sections done in 674 patients over a period of 30 years justify the authors' preference for subtemporal dorsal root section as the standard method of treatment.

J. G. R.

## ► INSTRUMENTATION IN ANESTHESIOLOGY

*By William H. L. Dornette, M.D., Professor and Head, Department of Anesthesiology, University of Tennessee College of Medicine, Memphis, and Verne L. Brechner, M.D., Assistant Professor of Anesthesiology, University of California School of Medicine, Los Angeles. 242 pages with 130 illustrations. 1959, Lea & Febiger, Philadelphia. $8.00.*

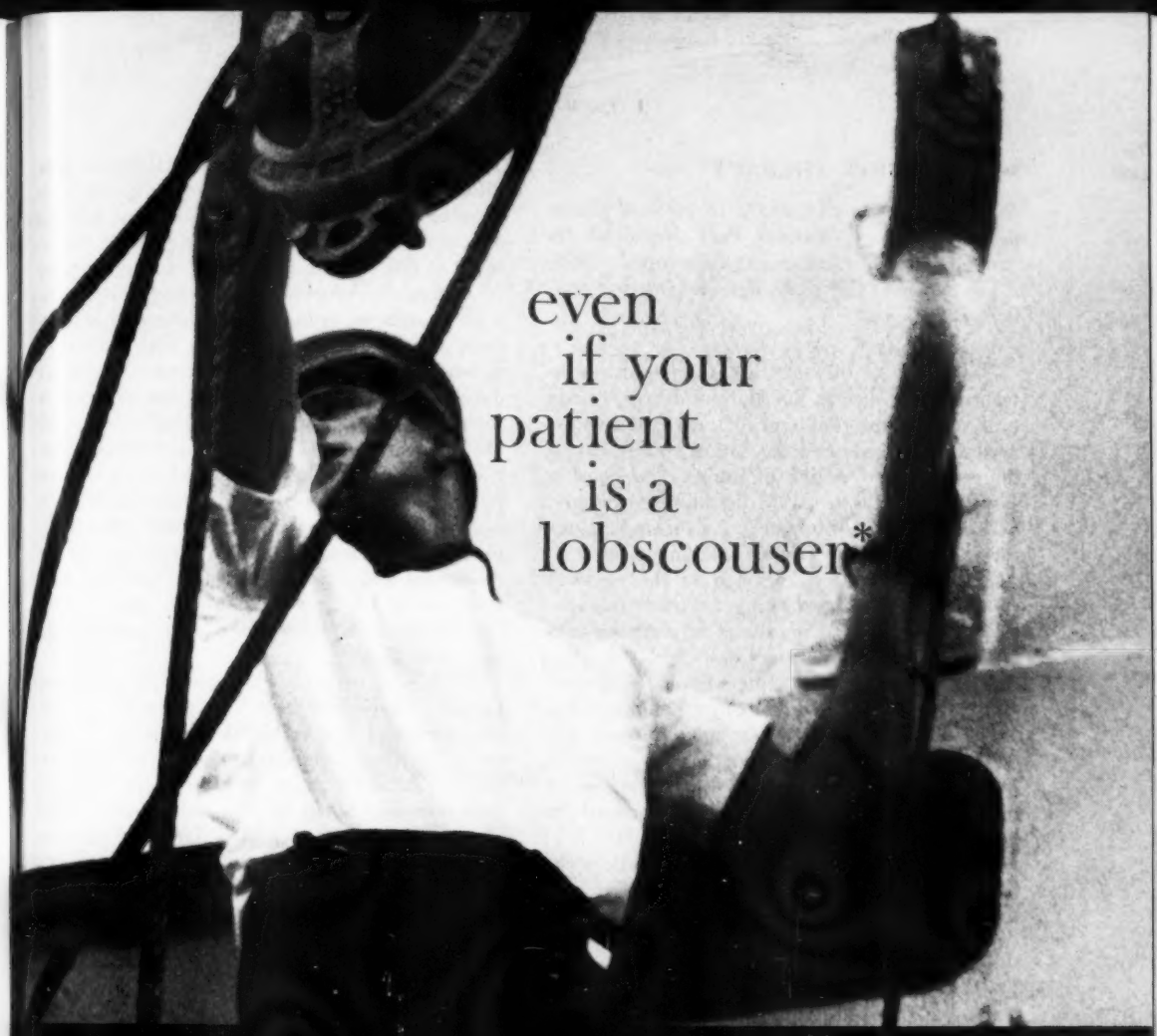
Anesthetic channels between blood vessels, which have been relatively neglected in the past 50 years, are discussed in this volume. The authors also explain from the standpoint of both neurology and anatomy why some vascular lesions of the brain do not always correspond with the blood supply as we know it anatomically. The explanation of why this seeming discrepancy occurs should be most welcome.

The timely presentation of the various instruments that can be used to advantage in the hospital, especially in the operating room, also has been very well done. Pictures and descriptions of instruments and diagrams of how they are used are presented. The anesthesiologist who avails himself of all these aids, especially in the operating room, will have a great advantage over the anesthesiologist who uses only his five senses.

This book should be examined by many people—certainly all those who are associated with the care of hospitalized patients. It will offer numerous ideas on management, nursing care, service, etc. The text is easily read and well indexed. The illustrations are sharp, and an extensive bibliography is presented.

J. S. L.

*(Continued on page A-196)*




'll be under way again soon, once he's on

# PARAFON®

AFLEX® + TYLENOL®)

muscle relaxation plus analgesia

d in arthritis

PARAFON®

ith Prednisolone

McNEIL

Neil Laboratories, Inc • Philadelphia 32, Pa.

prescribe PARAFON in low back pain—sprains—strains—rheumatic pains

Each PARAFON tablet contains:

PARAFLEX® Chlorzoxazone† ..... 125 mg.

Specific for skeletal muscle spasm

TYLENOL® Acetaminophen ..... 300 mg.

The analgesic preferred in musculoskeletal pain

*Dosage:* Two tablets t.i.d. or q.i.d.

*Supplied:* Tablets, scored, pink, bottles of 50.

Each PARAFON WITH PREDNISOLONE tablet contains: PARAFLEX® Chlorzoxazone† 125 mg., TYLENOL® Acetaminophen 300 mg., and prednisolone 1.0 mg.

*Dosage:* One or two tablets t.i.d. or q.i.d.

*Supplied:* Tablets, scored, buff colored, bottles of 36.

*Precautions:* The precautions and contraindications that apply to all steroids should be kept in mind when prescribing PARAFON WITH PREDNISOLONE.

*sailor

†U. S. Patent Pending

254A59

## ► RADIATION THERAPY

*By Walter T. Murphy, M.D., Director of Therapeutic Radiology, Roswell Park Memorial Institute, Buffalo. 1,041 pages, illustrated. 1959, W. B. Saunders Company, Philadelphia and London. $25.00.*

The author of this text, a radiotherapist at an institution devoted to the study of cancer, brings to the reader the results of his own extensive experience as well as information gained by a thorough review of the literature. The book is essentially on the technics of radiation therapy, and little emphasis is placed on the indications for radiation in the various malignancies.

The first chapter is devoted to the physical and biologic factors affecting radiation therapy. Actual step-by-step procedures in planning and administering treatment are described and illustrated. The remaining chapters cover the clinical and pathologic aspects of treating malignancies. The different methods of radiation therapy are described in detail, and examples are given of how they may be adapted to various stages of the disease. Radiation dosage is expressed in both roentgens and rads.

The numerous examples of therapeutic technics used in different clinical situations and in unusual cases should make this book of great value to the radiologist with limited experience. Students of radiation therapy and those engaged in the treatment of cancer also will find it useful.

The volume is profusely illustrated and has an extensive bibliography indexed according to subject and author; pertinent references are appended to the end of each chapter.

D. S. C.

## ► ORTHOPAEDICS

*By Samuel L. Turek, M.D., Attending Orthopaedic Surgeon, Weiss Memorial Hospital, Chicago. 906 pages with 600 illustrations. 1959, J. B. Lippincott Company, Philadelphia and Montreal. $22.50.*

Eighteen years ago, Dr. Turek began a systematic classification and filing of orthopedic information. This textbook represents his attempt to present this information between two covers.

The first six chapters of this book are devoted to basic sciences in orthopedics and to their application in the clinical aspects of the specialty. The second part covers general orthopedic conditions, with special emphasis on metabolic bone disease, infections, congenital deformities and developmental conditions. Of particular importance in this section is an entire chapter devoted to orthopedic neurology, including the neurologic aspects of orthopedic problems as well as basic neurologic diseases which the orthopedist is asked to recognize and to treat. A chapter devoted to peripheral vascular disease and to its application in orthopedics emphasizes both the medical and the traumatic aspects of arterial injuries. The third portion of the book presents regional orthopedic problems. The body is discussed by regions, with special importance placed on surgical anatomy, local pathologic conditions and suggested therapy. The final portion covers two special subjects: the role of radioisotopes in orthopedics and amputations and rehabilitation.

The simplicity and brevity of style employed by the author make it easy to grasp the principles presented and to use this book as a reference. The illustrations are adequate and informative; in some instances, they are more complete than normally would be expected in such a text. For its size, this book is well done and presents an amazingly complete coverage of the subject.

E. W. J.

## ► DIABETIC MANUAL

*By Elliott P. Joslin, M.D., Clinical Professor Emeritus of Medicine, Harvard Medical School, Boston. Ed. 10. 304 pages with 40 illustrations. 1959, Lea & Febiger, Philadelphia. $9.50.*

The new edition of this classic manual for diabetic patients is especially welcome at this time, since it contains information on the newer insulins and the oral hypoglycemic drugs. As in prior editions, a multitude of subjects of interest to diabetic patients are covered, including diet, insulin and its administration, exercise, marriage, complications of diabetes, and many others.

The physician should ask each patient who has diabetes mellitus to read a book of this type, because it will give the patient a better understanding of the disease and its management. This book also will be helpful to physicians, because it offers ready and simple answers to many of the questions asked by diabetic patients.

R. V. R.

*(Continued on page A-198)*

# *running noses* and open stuffed noses orally

# Triaminic®

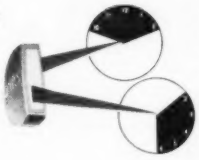
*the leading oral nasal decongestant*

- in nasal and paranasal congestion
- in sinusitis
- in postnasal drip
- in allergic reactions of the upper respiratory tract

*safer and more effective than topical medication*[1,2,3]

- systemic transport to all respiratory membranes
- provides longer-lasting relief
- presents no problem of rebound congestion
- avoids "nose drop addiction"

*Relief with Triaminic is prompt and prolonged because of this special timed-release action . . . beneficial effect starts in minutes, lasts for hours*



*first* — the outer layer dissolves within minutes to produce 3 to 4 hours of relief

*then* — the core disintegrates to give 3 to 4 *more* hours of relief

*Each TRIAMINIC Tablet provides:*
Phenylpropanolamine HCl .....50 mg.
Pheniramine maleate .....25 mg.
Pyrilamine maleate .....25 mg.

One-half of this formula is in the outer layer, the other half is in the core.

*Dosage:* One tablet in the morning, mid-afternoon and at bedtime.

*References:* 1. Lhotka, F. M.: Illinois M. J. 112: 259 (Dec.) 1957. 2. Fabricant, N. D.: E.E.N.T. Monthly 37:460 (July) 1958. 3. Farmer, D. F.: Clin. Med. 5:1183 (Sept.) 1958.

TRIAMINIC JUVELETS: Each timed-release Juvelet is equivalent in formula and dosage to one-half of a TRIAMINIC tablet, for the adult or child who requires only half strength dosage.

TRIAMINIC SYRUP is recommended for adults and children who prefer liquid medication. Each 5 ml. tsp. is equivalent to ¼ of a Triaminic Tablet. *Adults:* 2 tsp. 3-4 times a day; *children 6-12:* 1 tsp. 3-4 times a day; *children under 6:* in proportion.

SMITH-DORSEY • a division of The Wander Company • Lincoln, Nebraska

## ► SURGICAL PATHOLOGY

*By Lauren V. Ackerman, M.D., Professor of Surgical Pathology and Pathology, and Harvey R. Butcher, Jr., M.D., Associate Professor of Surgery, Washington University School of Medicine, St. Louis. Ed. 2. 1,096 pages with 1,114 illustrations. 1959, The C. V. Mosby Company, St. Louis. $15.00.*

A well-balanced, up-to-date, and fairly comprehensive outline of the broad field of surgical pathology is presented in this textbook. This second edition represents an extensive revision of the first and is a collaborative effort on the part of the surgical pathologist and the surgical colleague. The volume of both the text and the illustrations has been increased by approximately one-third. Entirely new sections include chapters on the healing of wounds and diseases of vessels by Dr. Butcher and a comprehensive outline of surgical pathology of the eyes and ocular adnexa by Dr. Zimmerman. The inclusion of basic surgical pathologic changes of eye and orbit, long neglected in textbooks of surgical pathology, is a welcome addition. In the other somewhat specialized fields, the section on nonneoplastic diseases of the skin has been revised by Dr. Robert Ogilvie, and the chapter on the central nervous system has been entirely rewritten by Dr. David E. Smith.

The authors have emphasized and illustrated the more commonly observed conditions; in general, they have provided sufficient detail on these subjects for most purposes. Less common lesions usually are briefly noted, but adequate and up-to-date references are provided. As in all textbooks, some subjects are treated more adequately than are others, undoubtedly a reflection of the personal interests and experience of the authors. Clinicopathologic correlation is emphasized throughout, and practical comments are provided on the application of newer technics in diagnosis, such as exfoliative cytology and aspiration biopsy. The authors provide a number of common-sense and sometimes amusing observations on the use of frozen sections. In each chapter they discuss the ease or difficulty of diagnosis by this method. A conservative attitude is properly emphasized. However, it should be noted that the accuracy and usefulness of the frozen-section technic in all areas of the body vary according to the experience and skill of the individual pathologist.

The book is beautifully illustrated. Photographs of gross materials are abundant and skillfully chosen, and the photomicrographs are well taken and carefully reproduced. A number of helpful charts and diagrams are included.

This book should be of great aid to the medical student and resident physician as an adjunct to textbooks on general pathology. It is recommended as an excellent source of information for the practicing surgeon or internist interested in surgical pathology.

L. B. W.

## ► SEX AND THE ADOLESCENT

*By Maxine Davis. 317 pages. 1958, The Dial Press, New York. $5.00.*

Physicians frequently receive requests from parents for the names of books that would be appropriate for the sex education of their children who are approaching puberty and adolescence. Unfortunately, many parents are not sufficiently prepared to educate their children on this subject, and, because of their own reticence in talking about these matters, they find it much easier to present the growing child with a book to explain many of the problems involved in growing up. This is such a book.

The author has written several previous books on medical and psychologic subjects. For 11 years she wrote a monthly medical article for *Good Housekeeping*, and she has contributed many articles to other national magazines. She has written this book primarily for young people, but, as she puts it, "It is also for those parents who feel the need of assistance in understanding some of the questions and problems that arise in young people's minds."

The first part is entitled "About boys," the second part "About girls," and the third "About boys and girls together." The various aspects of anatomy, physiology and social mores are discussed. The book is well written in that it is not too technical, and its language is aimed at the level of the adolescent. At times one gets the impression that the author tries to be too chummy with the adolescent to prove that she is on his side, but in general the book adequately fulfills its purpose—a purpose which would be much better fulfilled by the parent.

E. M. L.

*(Continued on page A-200)*

New . . . for the metabolic treatment of

# gout

# ANTURAN™

(sulfinpyrazone GEIGY)

**High Potency Uricosuric Agent**

By significantly increasing renal excretion of urate and thus lowering plasma uric acid, the new highly potent uricosuric agent ANTURAN strikes directly at the basic metabolic defect in gout.

Exceptionally high potency...4 to 6 times that of probenecid† ...is the outstanding characteristic of ANTURAN. The effectiveness of ANTURAN is retained indefinitely and tolerance to it is good.

Clinically, ANTURAN:

- Prevents formation of new tophi
- Causes gradual absorption of old tophi
- Relieves chronic pain
- Restores joint mobility

ANTURAN is not designed for the treatment of acute attacks for which BUTAZOLIDIN® is recommended. **Detailed Information On Request**

†Yü, T. F.; Burns, J. J., and Gutman, A. B. Arth. & Rheumat. 1:532, 1958.

ANTURAN™ (sulfinpyrazone GEIGY). Scored tablets of 100 mg. in bottles of 100.

BUTAZOLIDIN® (phenylbutazone GEIGY)

Geigy

Ardsley, New York

## ► TUBERCULOSIS AND OTHER COMMUNICABLE DISEASES

*Edited by J. Arthur Myers, M.D., Professor of Internal Medicine and Public Health, University of Minnesota Medical, Public Health and Graduate Schools, Minneapolis, with 25 contributors. 499 pages, illustrated. 1959, Charles C Thomas, Springfield, Illinois. $14.50.*

A rather elementary text on communicable diseases, this book is probably much too brief for even a medical student. Indeed, some textbooks for nurses contain more detailed information on communicable diseases than is found in this text. Furthermore, since only 60 pages are devoted to tuberculosis, the title of the book is somewhat misleading.

Not all communicable diseases are discussed. The subject of poliomyelitis is covered only from the standpoint of nursing care, and there is no discussion of the epidemiology or the recent progress in the immunization programs. Improper placement of emphasis is evidenced by the fact that an entire chapter is devoted to cat-scratch fever, whereas the problems associated with infectious mononucleosis are mentioned in scattered sections in only a sentence or two. Certainly, infectious mononucleosis is by far a greater problem than is cat-scratch fever.

Desirable features include interesting historical facts relating to the history of tuberculosis and bits of information on tuberculosis from the aspect of world health. The chapter on acute respiratory diseases is probably one of the most complete sections of the book, containing much useful information relating to diagnosis and treatment.

Y. S.

## ► A PRIMER OF WATER, ELECTROLYTE AND ACID-BASE SYNDROMES

*By Emanuel Goldberger, M.D., Lecturer in Medicine, Columbia University College of Physicians and Surgeons, New York. 322 pages, illustrated. 1959, Lea & Febiger, Philadelphia. $6.00.*

An excellent introduction to the complex subject of electrolyte and fluid balance, this book includes discussions of extracellular water, syndromes associated with water and sodium disturbances, syndromes due to disturbances in acid-base balance, and principles of fluid therapy. The section on disturbances in acid-base balance includes chapters on metabolic and respiratory acidosis and alkalosis, renal tubular acidosis, diabetic acidosis, salicylate poisoning, hyperpotassemia and hypopotassemia, primary aldosteronism and many other conditions.

In a book of this length, each discussion is necessarily brief and didactic. The text is well written, easy to read, and contains a number of illustrations and tables.

R. V. R.

## ► SURGERY OF THE EAR

*By George E. Shambaugh, Jr., M.D., Professor of Otolaryngology, Northwestern University Medical School, Chicago. 669 pages with 326 illustrations. 1959, W. B. Saunders Company, Philadelphia and London. $27.50.*

No one in the present generation of otologists with clinical experience beginning in the preantibiotic era can speak with more authority in this field than can the author of this textbook. Dr. Shambaugh has made many contributions to the literature during recent years.

This volume begins with an introduction to surgery of the ear, covering developmental and surgical anatomy, diagnosis, radiologic examination and principles of temporal bone surgery. The second part of the book is devoted to a discussion of surgery in infections of the ear. This section covers the pathology and clinical course of inflammatory diseases of the middle ear; surgical conditions of the auricle, external meatus and tympanic membrane; surgery on the mastoid for acute and chronic disease, and the meningeal and nonmeningeal complications seen in otitis media.

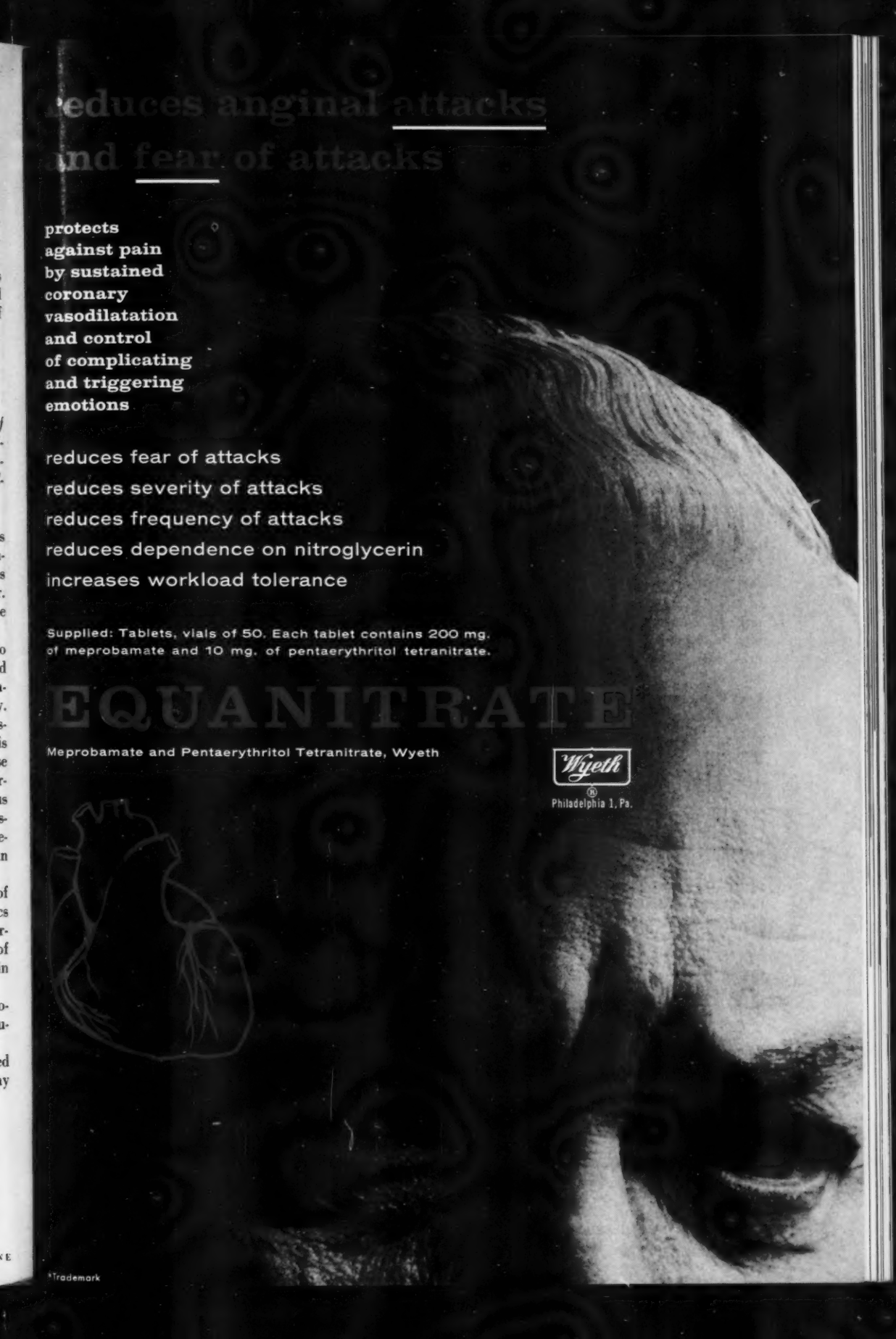
The discussion of the surgical correction of deafness includes information on the mechanics of hearing, closure of tympanic membrane perforations, tympanoplasty, and the diagnosis of otosclerosis and the indications for surgery in this condition.

Surgery of the facial nerve and surgical procedures for endolymphatic hydrops and for tumors of the ear also are covered.

This book should prove to be a much-needed and authoritative contribution to present-day literature on otologic surgery.

L. R. B.

*(Continued on page A-202)*


reduces anginal attacks
and fear of attacks
protects
against pain
by sustained
coronary
vasodilatation
and control
of complicating
and triggering
emotions
reduces fear of attacks
reduces severity of attacks
reduces frequency of attacks
reduces dependence on nitroglycerin
increases workload tolerance
Supplied: Tablets, vials of 50. Each tablet contains 200 mg.
of meprobamate and 10 mg. of pentaerythritol tetranitrate.
EQUANITRATE*
Meprobamate and Pentaerythritol Tetranitrate, Wyeth
Wyeth
Philadelphia 1, Pa.
*Trademark

## ► DISEASES OF THE NOSE, THROAT AND EAR

*Edited by Chevalier Jackson, M.D., late Honorary Professor of Laryngology and Bronchoesophagology, and Chevalier L. Jackson, M.D., Professor of Laryngology and Broncho-esophagology, Temple University School of Medicine, Philadelphia, with 61 contributors. Ed. 2. 886 pages with 645 illustrations, 16 color plates. 1959, W. B. Saunders Company, Philadelphia and London. $20.00.*

The first edition of this very popular reference textbook was published 15 years ago. Due to the many important advances which have occurred in the field of otolaryngology since that time, the editors undoubtedly have attempted to bring it up to date. However, in any reference textbook of this type to which so many authors contribute, some of the material may no longer be entirely current by the time the book is published.

There is more space allotted in this book to the management of acute and chronic infections of the ear than seems necessary in the present day. In addition, some of the illustrations are obsolete. Advances in the reconstructive measures now used for chronically damaged middle ear mechanisms are not considered, and the section dealing with stapes mobilization does not contain the most current information. These criticisms are not surprising, however, in view of the rapidly occurring advances in otolaryngology.

L. R. B.

**Books received are acknowledged in this department. As space permits, books of principal interest to our readers are reviewed more extensively.**

**Principles of Disability Evaluation.** By Wilmer Cauthorn Smith, M.D., Chief Medical Advisor, Oregon State Industrial Accident Commission, Salem. 210 pages. 1959, J. B. Lippincott Company, Philadelphia and Montreal. $7.00.

**Chemical Quantitation of Epinephrine and Norepinephrine in Plasma.** By William Muir Manger, M.D., Department of Medicine, Columbia University College of Physicians and Surgeons, New York, Khalil G. Wakim, M.D., Section of Physiology, and Jesse L. Bollman, M.D., Section of Biochemistry, Mayo Clinic, Rochester, Minnesota. 398 pages, illustrated. 1959, Charles C Thomas, Springfield, Illinois. $11.50.

**The Art of Relaxation.** By Herman S. Schwartz. Reprint edition. 212 pages, illustrated. 1959, Sessions Publishers, Elmhurst, New York. $3.00.

**The Chemistry of Heredity.** American Lecture Series. By Stephen Zamenhof, Ph.D., Associate Professor of Biochemistry, Columbia University College of Physicians and Surgeons, New York. 106 pages with 10 illustrations. 1959, Charles C Thomas, Springfield, Illinois. $4.25.

**The Kinetics of Cellular Proliferation.** Proceedings of the conference on Fundamental Problems and Technics for the Study of the Kinetics of Cellular Proliferation. Edited by Frederick Stohlman, Jr., M.D., National Institutes of Health, Bethesda, with 73 contributors. 456 pages, illustrated. 1959, Grune & Stratton, Inc., New York and London. $5.75.

**Handbook on Standard Nomenclature of Diseases and Operations.** Edited by Edward T. Thompson, M.D. and Adaline C. Hayden, C.R.L. 71 pages. 1959, The Blakiston Division, McGraw-Hill Book Company, Inc., New York, Toronto and London. $1.50.

**Peripheral Vascular Diseases;** an Objective Approach. By Travis Winsor, M.D., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine, Los Angeles. 845 pages with 435 illustrations. 1959, Charles C Thomas, Springfield, Illinois. $16.50.

**Home Care of the Child With Rheumatic Fever.** A guide for parents. Prepared and published by the American Heart Association, New York, 1959. 25 pages, illustrated. Copies are available from local heart associations.

**Intern's Manual.** By Arthur Bernstein, M.D., Assistant Medical Superintendent, Cook County Hospital, Chicago. Ed. 2. 308 pages. 1959, The Year Book Publishers, Inc., Chicago. $3.00.

**The Nature of Retirement.** By Elon H. Moore, Ph.D., late Professor and Head, Department of Sociology, University of Oregon, Eugene. 217 pages. 1959, The Macmillan Company, New York. $4.50.

**International Textbook of Allergy.** Edited by J. M. Jamar, M.D., Lecturer at the University of Louvain, Louvain, Belgium, with 31 contributors. 639 pages, illustrated. 1959, Charles C Thomas, Springfield, Illinois. $17.50.

**Mind If I Smoke?** By Harold Shryock, M.D., Professor of Anatomy, College of Medical Evangelists, Loma Linda-Los Angeles. 138 pages, illustrated. 1959, Pacific Press Publishing Association, Mountain View, California. $0.50.

**Preventive Medicine.** Principles of prevention in the occurrence and progression of disease. Edited by Herman E. Hilleboe, M.D., Commissioner of Health, and Granville W. Larimore, M.D., Deputy Commissioner of Health, State of New York, Department of Health, Albany, with 31 contributors. 731 pages with 59 illustrations. 1959, W. B. Saunders Company, Philadelphia and London. $12.00.

**European Technical Digests.** A monthly information service for business and industry, consisting of condensations of articles published in approximately 1000 European journals. Published by The European Productivity Agency of the Organisation for European Economic Cooperation, Paris, France. $12.00 per year.

# Financial Planning

*A monthly service* dealing with the basic problems of increasing your net income and building personal capital . . . *in the face of today's high tax structure*

*prepared by the*

J. K. LASSER INSTITUTE

*for*

Postgraduate Medicine

OCTOBER 1959


In Providing For His Retirement - can the doctor make use of a qualified retirement plan established by a professional partnership of which he is a member? A partner is an owner, not an employe, of his partnership. Thus, normally he can't qualify for benefits available through a tax-qualified retirement plan established by his partnership. However, the partner in a commercial partnership is able to bring himself within a retirement plan by converting business operations from partnership to corporate form. In that way, he becomes an employe. Now, the former partner-owner is an owner-employe of his corporation. As an employe, he also can get the tax benefits of any employe-retirement plan his corporation establishes.

Consider now the situation of a doctor. Under the laws of his state, doctors are prohibited from practicing in corporate form. A professional partnership can't be converted to a corporation. Doctor Jones is a member of a professional partnership. Is there any way he can qualify for benefits under a qualified retirement plan his partnership is setting up? This method has been given approval.

The doctors, members of the professional partnership, switch from partnership form to association form. An association is not a legal corporation. However, for tax purposes it is treated as a corporation. Doctor Jones is a partner no longer. He is now an owner-employe of his association. As an employe, he can qualify for retirement benefits under his association's retirement plan. A few years ago, eight doctors operating a clinic made this switch from partnership to association form. Thereafter, the eight doctors plus three other individuals qualified as employes for pension benefits under their association's qualified retirement plan (Kintner, 216 F. 2d 418). More recently a group of doctors in Texas made similar switch to qualify for similar benefits with court approval (Galt, Tex., Dallas Div., 7/27/59).

What Are The Tax Benefits Available - through this conversion of a professional partnership to professional association? They can be substantial.

(1) Partnership income formerly taxed currently to the partners becomes association income. To the extent that the association contributes to the retirement plan, that income becomes tax deductible.

(2) Amounts contributed by the association for the benefit of the doctors compound tax free. A 4% return on such contributions remains a 4% return. It is not reduced by current taxes to a 3% or a 2% return, or even less. Over a period of time, this accelerates the rate of savings for the benefit of the doctors.

(3) When the doctor reaches retirement age, he can withdraw the large amounts contributed to the retirement plan for his benefit in a lump sum. If he does, he owes only a capital gains tax on such withdrawal. Tax couldn't exceed 25% and might be as low as 10% as a result.

(4) If he dies prematurely before he can receive his retirement benefits, those amounts paid directly to a beneficiary (e.g., his wife) are exempt from estate tax.

Does Good Will Exist In A Professional Partnership? There is conflict among legal authorities as to whether or not it does. The argument against existence of such good will is that the value of a professional practice in excess of physical assets is due solely to professional skill. Such skill is not an asset which can be sold or traded. Yet the recognition of good will in a professional practice can have important financial, legal, and tax consequences to the professional man.

For Federal tax purposes, the existence of good will in a professional practice has been recognized. Thus, one professional man was permitted to sell good will attributable to his practice and secure tax protection on such sale. However, recognition of good will for Federal tax purposes doesn't mean it will be recognized for all purposes. State law rather than Federal law may control in a particular situation and state law may deny existence of good will.

"A professional partnership, whose reputation depends upon the individual skill of the members, has no good will to be distributed as a firm asset on its dissolution." So held a higher New York State court to the financial detriment of one member of a professional partnership. The partnership consisted of a number of members. Because of disagreements, it was decided to dissolve the partnership. After dissolution of the partnership, the partners, with the exception of one, formed a new partnership.

The excluded partner brought suit for an accounting. He wished a court to determine whether professional income and any fees of the new partnership were "attributable to his contribution to the good will of the (old) partnership." A lower court decided that he was entitled to such determination. However, on appeal,

the higher court decided that good will is not ordinarily attributable to a professional partnership. As a result his suit for accounting was dismissed.

* * * * *

Estate Taxes Running Into The Millions Of Dollars - are needlessly incurred because individuals who will be leaving comparatively small estates don't realize the importance of setting up an estate plan during life. If total value of interests in life insurance, residence, professional practice, investments, etc., will run more than $60,000, an estate tax may be due on death. Yet if a husband leaves property to his wife in such a way as to qualify for the so-called marital deduction, he could leave an estate of $120,000 without incurring any estate tax. While this marital deduction provision has been part of the tax law since 1948, many husbands fail to take advantage of it.

Official statistics released by the Internal Revenue Service for the latest year confirm that. More than 25,000 estate tax returns were filed for estates running from $60,000 to $120,000. Approximately 50% of those estates did not have to pay any estate taxes because of the marital deduction. However, estate taxes were incurred by the remainder. Many of the latter estates were those of married individuals who failed to leave property to their wives in a way which would have eliminated the tax. Such failure added millions of dollars to tax revenues at the expense of surviving spouses.

A Mistake In Insurance Elections - is one reason why estate tax marital deduction frequently is lost. As a result, estates (only slightly in excess of $60,000) require an estate tax payment.

A professional man takes out insurance on his life, names his wife beneficiary. Under the policy, he can elect to have payment to his wife after his death made in one of these ways: (1) lump sum, (2) for her life, (3) over a fixed period of years, (4) at a fixed rate until paid out, or (5) for her life with a certain number of payments guaranteed. Under the last three elections, husband will name a second beneficiary - usually children - to take what may be left if his wife dies before insurance proceeds are completely paid out. By selecting the contingent beneficiary, husband deprives his estate of any marital deduction for insurance left to the wife.

By proper estate planning, husband could make any of the above elections and still preserve the marital deduction for estate tax savings. The husband makes one of the elections during life. However, he names his wife's estate contingent beneficiary or he

gives her the right to name the contingent beneficiary. In either case, any unpaid insurance proceeds remaining on the death of the wife would probably go to children - either through inheritance or because she names them contingent beneficiaries.

* * * * *

Are Entertainment Expenses Incurred By The Doctor - ever deductible for tax purposes? The Internal Revenue Service has again conceded that a doctor may deduct entertainment expenses if "such expenses are ordinary and necessary (professional) expenses and clearly related to the production of (professional) income." Warning: While this latest announcement has been reported as one favorable to the doctor, the language of the ruling attempts to limit deduction. Here are some of the highlights from the ruling.

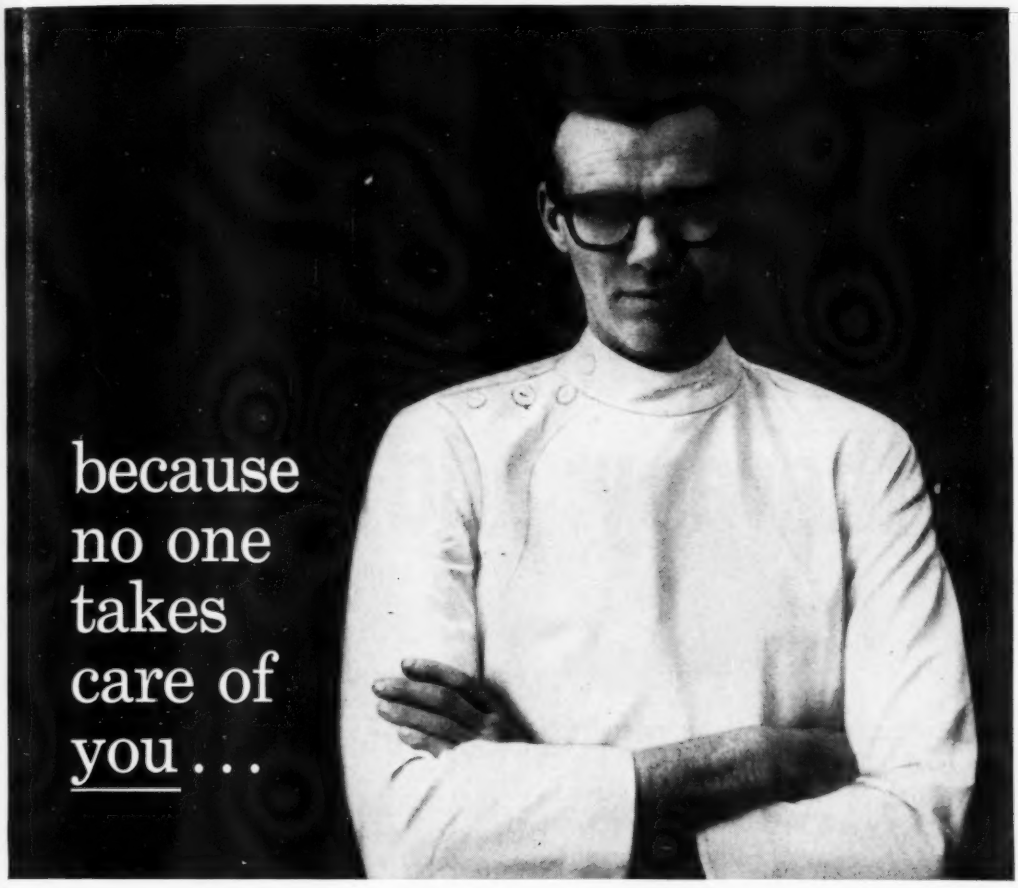
Except in the case of industrial physicians, entertainment of individuals who are not doctors will not ordinarily qualify for deduction. In other words, it will be the exceptional case where an agent will allow costs incurred in entertainment of patients. Even where a sound professional motive might be behind entertainment, the doctor will have difficulty in securing deduction unless he can show (1) a specific purpose aside from any personal motive in entertaining, (2) that a percentage of his patients are received as referrals, (3) why he could reasonably expect additional income from entertainment of the individuals actually entertained, and (4) the extent to which referrals were actually received (if they were) from those individuals entertained.

Other criteria which will be used in considering deduction of entertainment expenses include nature of the practice of the doctor incurring the expense and whether or not other doctors in the same type practice in the locality have entertainment expenses.

When A Doctor Purchases The Practice - of a deceased professional man, may he take tax deductions for his payments? A doctor purchased the practice of a deceased doctor from his widow, including the good will together with the use of records under a contract calling for installment payments. He was not allowed any deduction for installment payments. A court held that they were nondeductible capital expenditures, reflecting good will of the practice.

Note that while the doctor purchasing the practice was not allowed any tax benefit, recognition of the existence of the good will did have tax value to the widow. Good will in the hands of a seller is a capital asset. As a result, the widow could report income realized on the sale as capital gain. Tax on such income realized by the widow couldn't exceed 25%.

Now available at cost—$1.50—3-ring loose-leaf binder to hold 24 monthly Lasser reports. Made of blue simulated morocco grain leather; non-soil finish with embossed cushion edge. Send check with name and address to POSTGRADUATE MEDICINE, Essex Building, Minneapolis 3, Minnesota.




## *you need the protection of* TRUE SECURITY

Since you are probably self-employed, you can't look forward to provided-for retirement benefits as do men in other careers. You must provide for yourself. In this, as in so many financial areas, your profession presents difficulties which require special solutions on your part.

A wise way to cope with your particular financial problems is to discuss them with your Mutual Benefit Life man. Let him develop a comprehensive, individual plan for your TRUE SECURITY—a plan which takes into account all the unusual financial aspects of your career. His thorough understanding of your needs, both now and to come, is the result of Mutual Benefit Life's 114 years of service to the medical professions.

Get in touch with your Mutual Benefit Life man soon. With no obligation to you he will provide an economical plan to give you and your family the unique benefits of TRUE SECURITY, starting now!

**MUTUAL BENEFIT**
*The* **LIFE** *Insurance Company for TRUE SECURITY*

## MUTUAL BENEFIT LIFE'S FINANCIAL PLANNING FOR YOU AND YOUR FAMILY

*Send this coupon for your free copy of an analysis of the medical profession's financial problems and their solution.* This is not only an insurance booklet *but an overall handbook showing how you can keep more of your earnings. The use of this coupon does not obligate you in any way.*

THE MUTUAL BENEFIT LIFE INSURANCE COMPANY
AGENCY DEPT. PG-4
NEWARK 1, NEW JERSEY

Name.....

Address.....

City..... State.....

# For the best results from antihypertensive therapy: add Esidrix™

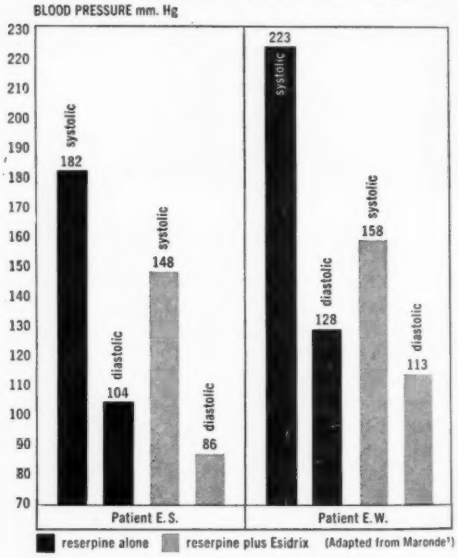
(hydrochlorothiazide CIBA)

**THE ANTIHYPERTENSIVE POTENTIATOR**

Esidrix, through its unique effect on body salts,* provides a physiologic environment in which antihypertensive drugs work best. Thus Esidrix, when added to any treatment program:

1. Safely reduces blood pressure to the lowest levels yet achieved with oral therapy.
2. Often reduces blood pressure in patients resistant to previous therapy.
3. Minimizes side effects by reducing dosage requirements of other drugs.
4. Promotes diuresis in patients with edema.

Potentiating Effect of Esidrix on Serpasil




*Esidrix is at least 10 times more active than chlorothiazide and greatly increases sodium and chloride excretion; however, it has no more effect on potassium excretion than does chlorothiazide.

# ...Pathibamate®

meprobamate with PATHILON® tridihexethyl chloride Lederle

*for relieving tension and curbing hypermotility and excessive secretion in G. I. disorders*

**PATHIBAMATE** combines two highly effective and well-tolerated therapeutic agents:

**meprobamate (400 mg. or 200 mg.)**—a tranquilizer and muscle-relaxant widely accepted for the effective management of tension and anxiety

**PATHILON (25 mg.)**—an anticholinergic long noted for producing prompt symptomatic relief through peripheral, atropine-like action, yet with few side effects

*now available...*

## *PATHIBAMATE-200 Tablets*

200 mg. meprobamate • 25 mg. PATHILON

*for more flexible control of G. I. trauma and tension smooth, sugar-coated, easy-to-swallow*

PATHIBAMATE-400 and PATHIBAMATE-200 are indicated for duodenal ulcer; gastric ulcer; intestinal colic; spastic and irritable colo ileitis; esophageal spasm; anxiety neurosis with gastrointestinal symptoms and gastric hypermotility.

**Supplied:** **PATHIBAMATE-400**—Each tablet (yellow, 1/2-scored) contains meprobamate, 400 mg.; PATHILON tridihexethyl chloride 25 mg.

**PATHIBAMATE-200**—Each tablet (yellow, coated) contains meprobamate, 200 mg.; PATHILON tridihexethyl chloride, 25 mg.

**Administration and Dosage:** **PATHIBAMATE-400**—1 tablet three times a day at mealtime and 2 tablets at bedtime.

**PATHIBAMATE-200**—1 or 2 tablets three times a day at mealtime and 2 tablets at bedtime.

Adjust dosage to patient response.

**Contraindications:** glaucoma; pyloric obstruction, and obstruction of the urinary bladder neck.

Lederle LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

# The Countryside of William Withering

HOWARD B. BURCHELL*

*Mayo Clinic and Mayo Foundation, Rochester, Minnesota*

PREDICATED on the premise that other physicians might have thought of visiting the English countryside where Withering lived and practiced, I am attempting to transfer to writing my own experiences on such a journey. The excellence of this English practitioner in both medical ethics and science has been attested to by contemporary writings and by his biographers; and there are many reasons why he should have become a figure to interest the medical student, apart from his role in scientifically studying and popularizing the utilization of foxglove for the treatment of dropsy. My interest in Withering may have been in part an inheritance from a hero figure, Sir William Osler, who highly regarded Withering as a practitioner; in common with my medical classmates, I idealized Osler. The fact that Withering believed that the time spent in acquiring multilinguistic ability was a relative loss of time also has piqued the interest of the student struggling with his scientific German and French. Withering's ethical defense of his practices, when accused of negligence in the cases of Mrs. Gresley and Mrs. Houlston, and the scurrilous attacks at that time by Robert Darwin, son of Erasmus Darwin, are stories that compete favorably with fiction. It is to be wondered whether Charles Darwin, who described his father as the most kindly of men, could have had access to the uncharitable dialectic in his father's letters to Withering.

HOWARD B. BURCHELL

In retrospect, the proper diagnoses in the Gresley and Houlston cases remain a challenge. Mrs. Gresley died nearly a month after her first confinement, presumably of an infection; the chief instigator of complaints apparently was her surgeon-husband. It is of general interest in regard to this case that Withering had had considerable experience with streptococcal infections, having described the Birmingham scarlet fever epidemic in 1778, three years before he was a consultant in Mrs. Gresley's illness. To give to the American reader historical perspective, Mrs. Gresley died 62 years before Oliver Wendell Holmes gave his first address on the contagiousness of puerperal fever; in addition, it must be recognized that Mrs. Gresley's illness was far too prolonged to be labeled simply as puerperal fever. Holmes, incidentally, shares the same birth year (1809) as Charles Darwin.

Withering diagnosed the illness of Mrs.

*(Continued on page A-230)*

*Section of Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

WHENEVER COUGH THERAPY IS INDICATED

# Hycomine SYRUP

THE *complete* Rx FOR COUGH CONTROL

*cough sedative / antihistamine / expectorant*

- relieves cough and associated symptoms in 15-20 minutes
- effective for 6 hours or longer
- promotes expectoration
- rarely constipates
- agreeably cherry-flavored

Each teaspoonful (5 cc.) of HYCOMINE contains:

| | | |
|---|---|---|
| Hycodan® | | |
| Dihydrocodeinone Bitartrate (Warning: May be habit-forming) | 5 mg. | 6.5 mg. |
| Homatropine Methylbromide | 1.5 mg. | |
| Pyrilamine Maleate | | 12.5 mg. |
| Ammonium Chloride | | 60 mg. |
| Sodium Citrate | | 85 mg. |

Supplied: As a pleasant-to-take syrup. May be habit-forming. Federal law permits oral prescription.

Endo® *Literature on request*

ENDO LABORATORIES Richmond Hill 18, New York

U.S. Pat. 2,439,609

Houlston, a resident of Wellington, as hepatitis. This diagnosis would seem to fit present-day concepts of the disease, but the vituperative attacks on Withering by Robert Darwin may have no parallel in the history of medical controversy.

The life of Withering engenders a feeling of historical contemporariness in the American reader, since he practiced during the American Revolution, having entered practice in Birmingham in 1775. He also was actively engaged in varied intellectual fields, and he belonged to the Lunar Society, whose membership included Priestley, Watt, Erasmus Darwin, Boulton and Wedgwood and to which Benjamin Franklin is said to have lent his presence on occasion. The activities of the Lunar Society seem particularly significant when one follows through with the history of that organization and learns of its difficulties during the Birmingham riots at the time of the French Revolution. My sophomoric delight in puns also may well have early focused my attention on Withering when I read the remark made during his last illness, "The flower of English physicians is indeed Withering."

Roddis's[1] biography of Withering has been available for some time; however, the more detailed biography written more recently by Peck and Wilkinson[2] seems likely to be established as a standard source of authoritative information on Withering's life.

For the medical historian, the counties of Shropshire, Staffordshire and Warwickshire are a veritable dreamland in which to try to recapture the past, traveling the paths of the famous Charles Darwin* (the grandson of both Wedgwood and Erasmus Darwin) and of Withering. Priestley, too, has been of particular interest to me, because of my interest in the development of the Unitarian faith in the United States, and especially in its espousal by Thomas Jefferson. The physician traveling in this area has the opportunity of visiting the modern Queen Elizabeth Hospital and the Birmingham Medical School, which is close to Edgbaston Church, where Withering was buried, and Edgbaston Hall, where he lived. In the square in Birmingham there are statues of Priestley and Watt, but I saw no statues of the other illustrious members of the Lunar Society. It is of some interest that apparently no medallion of William Withering was made; this might be explained by the fact that Josiah Wedgwood, being a close friend of Erasmus Darwin, might not have condoned it because of the latter's antipathy to Withering. Fertig[3] stated, "The medallions of people he [Wedgwood] knew take on added significance because we may be fairly certain that they received the approval of his critical eye." He also noted that "the favorite Aesculapius" of the Wedgwood family was Erasmus Darwin, who practiced at that time in Litchfield, placed between Birmingham and the pottery towns.

I do not know of any medical historian who, since Wilkinson's death, has had a prime interest in Withering, but, to me, one advantage of publishing these notes is the possibility of beginning a correspondence with persons who share this interest. By tourist standards, a week in the Birmingham area might be considered a reasonable length of time, but for a student of the personages who were living in this area 200 years ago and later it obviously is inadequate. My visit was in the second week of June, and at this time the foxglove was not yet in flower in the area. I was attuned to its recognition, however, by the fact that there were large beds of it in full flower along the Victoria embankment in London before that time. As an avid tourist-photographer I photographed these beds from near and far. This foxglove had been planted as a multicolored bed, and in the plots that I saw the purple variety was in the minority. I purchased seeds of the foxglove in Birmingham and in two villages, but all were packaged as mixed varieties. A curious coincidence happened the first morning I awoke in the home of an English physician: The curtains of the bedroom, drawn but transilluminated by the rising sun, showed purple foxglove in the print, and of interest was the fact that my charming hostess had not realized the nature of the flower in the print

*(Continued on page A-232)*

*The reader may wish to refer to Charles Darwin's autobiography or to a partial reprinting of it in "Chronicle of a misspent youth." Natur. Hist. 67:324 (June-July) 1958.

New reinforced therapy from Schering for seasonal asthma and allergic dermatoses

# Polanil

What's its name?

What is it?

POLANIL is dextro-chlorpheniramine maleate (Polaramine® Maleate) — the closest to a perfect antihistamine and dexamethasone (Deronil®) — today's lowest dosage corticosteroid.

What's its rationale?

What are its advantages?

What's its dosage?

How is it supplied?

POLARAMINE: the closest to a perfect antihistamine
DERONIL: today's lowest dosage corticosteroid
POLANIL

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

®T. M. EN-1427-1

Schering

or the special type of welcome it gave to me.

After driving leisurely through Wales we (my wife and I) started our Withering pilgrimage proper at Shrewsbury, in Shropshire. This town was the birthplace of Charles Darwin; he had been an avid hunter in the surrounding countryside in his youth. We stayed at The Lion, where Darwin had stayed the first night on his return to Shrewsbury by coach after debarking from the Beagle at Falmouth.

From Shrewsbury it was an easy and pleasant drive to the village of Withering's birth, Wellington. This is now a moderate-sized town, and the present church, which I believe stands on the site of the one where Withering was baptized in 1742, was built in 1790. The church is attractive; it stands on rising ground near the middle of the town and bears the following inscription over the doors: "All seats in this church are free and unappropriated forever. April 23, 1866." From Wellington the drive to Stafford, the town where Withering established his first practice, was through beautiful English countryside where hawthorn, rhododendrons and lupines were in bloom. Stafford is an attractive town.

Of casual interest during my visit to Wellington was my experience of asking for an extra copy of Peck and Wilkinson's biography at a pleasant, modern bookstore. I found that the proprietor did not know anything about the biography or indeed anything about this famous physician who had lived in his town. One tends to expect all Englishmen to be historians of their community, and, indeed, this seems usually to be the case.

Being interested in fly-fishing, I had a double interest in Stafford, which is the birthplace of Izaak Walton and which has a museum in his memory. The southern approach to Stafford was particularly attractive, and the road to Birmingham excellent, although the traffic was moderately heavy. With various road maps, we tried to calculate where Withering might have driven to see Mrs. Gresley and where near Bilston he fractured his collarbone when his carriage overturned. The industrialization of the area and multiple roads combined to defeat our endeavor. We did drive on the more rural roads toward Bridgnorth, where Withering was supposed to have seen a woman of Shropshire who was very ill with dropsy. It was from this case that he supposedly obtained knowledge of the remarkable disappearance of the edema following use of an old recipe. He stated, "It was not very difficult for one conversant with these subjects to perceive that the active herb could be no other than the foxglove."

Through the courtesy of Professor Arnot of the University of Birmingham, we were able to stay at the University Staff House, which was within walking distance of Edgbaston Church. From our window we could look across the botanical gardens and small lake to the Edgbaston estate, which had been leased by Withering and now is a golf course. The house is much as pictured in the biographies, standing on a mound overlooking a broad expanse of the present golf course. In the picture dated 1930 in Peck and Wilkinson's biography, vines cover most of the house to the third story, but this year only small isolated vines are growing. The shrubs were flowering at the time of our visit, being a brilliant dark blue, and we were informed that they were *Ceanothus*. While attempting to learn more of the nature of this plant from American books, I read that the leaves of the American variety *C. americanus* (New Jersey tea) were used as a substitute for tea during the American Revolution, as it was unpopular to use oriental tea brought in by English ships.

At the time of our visit I did not see any digitalis plants, and I understood a recent cold winter had killed many. There undoubtedly were some in the garden, as the biographers have stated: "Foxglove still bloom in Edgbaston Hall garden, the descendants of the plants which William Withering placed there and from whence he sent seeds to America."

In the Birmingham Medical School, there is a reproduction of the portrait of Withering by Von Breda. My amateur's eye was unable to tell it from the original, which I had viewed a fortnight previously in Stockholm. The Von Breda portrait, showing an alert, sharp-featured man holding in his lap foxglove plants

*(Continued on page 234)*

# *Now*—All cold symptoms can be controlled

# Tussagesic

*timed-release* tablets

*Controls congestion*
with Triaminic,[1,2,3] the leading oral nasal decongestant.

*Controls aches and fever*
with well-tolerated APAP, non-addictive analgetic[4] and excellent antipyretic.[5]

*Each TUSSAGESIC Tablet provides:*

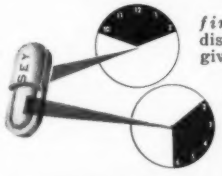
| | |
|---|---|
| TRIAMINIC® | 50 mg. |
| (phenylpropanolamine HCl | 25 mg. |
| pheniramine maleate | 12.5 mg. |
| pyrilamine maleate | 12.5 mg.) |
| Dormethan (brand of dextromethorphan HBr) | 30 mg. |
| Terpin hydrate | 180 mg. |
| APAP (N-acetyl-p-aminophenol) | 325 mg. |

*References:* 1. Lhotka, F. M.: Illinois M. J. 112:259 (Dec.) 1957. 2. Fabricant, N. D.: E.E.N.T. Monthly 37:460 (July) 1958. 3. Farmer, D. F.: Clin. Med. 5:1183 (Sept.) 1958. 4. Bonica, J. J.: in Drugs of Choice, Mosby, St. Louis, 1958, p. 272. 5. Dascomb, H. E.: in Current Therapy, Saunders, Phila., 1958, p.78. 6. Bickerman, H. A.: in Drugs of Choice, Mosby, St. Louis, 1958, p.547.

*Controls cough centrally*
with non-narcotic Dormethan, possessing "amply demonstrated" antitussive activity,[6] as effective as codeine.

*Liquefies tenacious mucus*
with terpin hydrate, classic expectorant.

***Prompt and prolonged relief because of this special "timed release" design:***



*first* — the outer layer dissolves within minutes to give 3 to 4 hours of relief

*then* — the inner core releases its ingredients to sustain relief for 3 to 4 more hours

*Dosage:* One tablet in the morning, midafternoon and at bedtime. Pediatric dosage chart for Tussagesic Suspension available on request.

*TUSSAGESIC SUSPENSION* provides palatability and convenience which make it especially attractive to children and other patients who prefer liquid medication.

SMITH-DORSEY • a division of The Wander Company • Lincoln, Nebraska

in bloom, had not been on exhibit in the Stockholm museum, but Dr. Nylin,[4] also a student of Withering lore, arranged with the director for us to see it. Of interest to collectors may be the differences in the foxglove plant as it appears in the frontispiece of the first edition of Withering. In some copies it is colored; in others it is not. The edition with the colored frontispiece that I saw was in the library of Dr. Evan Bedford[5] in London. Color printing was of course unknown in 1785, but in some copies of the book the plate was hand-colored very skillfully.* The plate itself was taken from "Flora Londinensis," by William Curtis.

The scientific museum in the city of Birmingham was less interesting than I had expected, and very little in the way of original machinery was on exhibit. In the art gallery I was intrigued by a portrait of a dog, being an owner of retrievers; my interest came chiefly from the fact that in the background and to one side was a beautiful painting of the purple foxglove. The painting, I believe, was on loan and was called "Ringwood, a Foxhound"; it was painted by George Stubbs in 1792.

Edgbaston Church is very attractive. It sits above the level of the roadway and in the old cemetery; at the time of my visit there, the scattered rhododendrons were in full bloom. On the inside of the right wall of the church is an engraved tablet entitled "Sacred to the Memory of William Withering, M.D., F.R.S., Born on March 28, 1741 and Died October 6, 1799, age 58 Years." The title is followed by poetry extolling his virtues (the poetry itself being of doubtful merit), and below appears the staff of Aesculapius with a branch of the foxglove and a branch of the herb of the genus *Witheringia*, to which he had given his name.

*The facsimile edition, limited to 250 copies and printed for the Broomsleigh Press, London, has the colored frontispiece and is the reference text available in the Mayo Clinic Library. It is interesting that the frontispiece showing the plant reveals the plant in mirror relationship to the frontispiece photographed in the Peck and Wilkinson biography. The color illustration on the cover and jacket of the book shows a reproduction of the frontispiece of Withering's book, but the stem of the plant is intact rather than interrupted and offset.

From Birmingham it was a short distance to Warwick Castle, still in traditional foxglove countryside, and thence to Stratford on Avon where there is much to remind one of the past and to relate the past to the future.

This communication pretends in no way to add to Withering's biographic essays, but I hope it will convey a type of satisfaction that a person may enjoy while visiting the countryside of a man whose biography has been presented in interesting detail. Those who wish to know of the many interests, scientific communications, and problems of practice of this outstanding physician are referred to Peck and Wilkinson's biography. Foxglove undoubtedly had been used by others prior to Withering's time, as he indeed pointed out in his monograph, but the credit for its rational use seems securely related to his practices and reports.[6] One may justifiably repeat a statement from his account of the foxglove: "In spite of opinion, prejudice or error, time will fix the real value upon the discovery and determine whether I have imposed upon myself and others, or contributed to the benefit of science and mankind."

My first visit to Withering's countryside took place figuratively and literally in a blackout, when I arrived by truck at Stone, where there was an American Air Force replacement camp 15 years ago during the war. My second visit, described herein, may be called an enlightenment; my hoped-for third visit I would wish to be associated with a maturation of medical historic interests in the area.

## REFERENCES


1. Roddis, L. H.: William Withering: The Introduction of Digitalis Into Medical Practice. New York, Paul B. Hoeber, Inc., 1936.
2. Peck, T. W. and Wilkinson, K. D.: William Withering of Birmingham. Baltimore, The Williams & Wilkins Company, 1950.
3. Fertig, H. H.: Josiah Wedgwood, medallions and physicians. Bull. Hist. Med. 28:127-139 (March-April) 1954.
4. Nylin, G.: William Withering—a bicentenary tribute. Am. Heart J. 25:285-297 (March) 1943.
5. Bedford, D. E.: Personal communication to the author.
6. Fulton, J. F.: Charles Darwin (1758-1778) and the history of the early use of digitalis. Bull. New York Acad. Med. 10:495-506 (August) 1934.

Ortho

while they are planning
their family

they need your help
more than ever

the most widely prescribed contraceptive

WHENEVER A DIAPHRAGM IS INDICATED

26259

# DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

**Aug. 1**—The White Sox continue magically to come from behind in the ninth inning. In the evening came Richard Frey, celebrated exponent of bridge, with his beautiful Mable to dine. And after that to the Hilton where players at 500 tables sought master points. Here met Harry Fishbein, who wears a different beret each session, according to how he feels. Also kibitzed behind the famous actuary Oswald Jacobi, who seemed to take his bridge lightly, but plays it well. Most of the players had on their faces a tensity which seemed well-nigh like a dream state. But the real champions, Schenken, Charles Goren, Helen Sobel, Becker, Easley Blackwood, Charles Solomon and many more, jested with old Pepys and seemed to take it as a game.

**Aug. 2**—In the afternoon to see the Sox again victorious. Then late to supper with the Friedells, and to the Edgewater to see Groucho Marx in "Time for Elizabeth," a light play about retiring in which he was superb with his perfect sense of timing, but the rest of the cast was abrupt and loud.

**Aug. 3**—At the desk with a variety of visitors planning for lectures in the months to come. Now the British magazines come with few pages, and the printers' strike is apparently in earnest for weeks to come. *Lancet* announces it will stop printing in Germany.

**Aug. 4**—To Don McNeill's Breakfast Club for my radio performance and met there Fred Perry, the once great Australian tennis player, and we reminisced about the famous Bill Tilden. And Perry said he still plays tennis but that the court now seems wider and longer than it used to be. In the afternoon to golf with Maurice and Bernice Goldblatt.

**Aug. 5**—Early came Dr. Nagai, distinguished pediatrician of Kyoto, to see La Rabida and the University. Then came Cowdry from St. Louis and we talked about our mutual projects, after which with both to the Quadrangle Club for luncheon. Here discovered that Cowdry speaks Chinese but that Japanese is so different that common understanding is impossible. In the afternoon to Hancock in West Virginia by B. & O. Capital Limited, which made a special stop just for me. The train, now down to just a half-dozen cars, was only half occupied: during the war, when I took it so frequently, it was a dozen cars long and most times not a space was to be had. But the dining car still deserves a special commendation for about the best food that transportation affords.

**Aug. 6**—At Hancock at 6:30 A.M. came a red-headed lady taxi driver to meet old Pepys, and so to the Park View Inn until noon, when came Leighton Pratt and Mr. Dux of the Pennsylvania Sand Glass Company to lunch. Then to view the hospital, which is to be rebuilt and enlarged. In the evening to dine in the high school gymnasium, where Lacy Price presided and Drs. Tobias, Fix and Detherage spoke, as did old Pepys. Then driving some 85 miles to Washington with Bill Haney and family, and then flew from the airport at 12:25 A.M. for Chicago.

**Aug. 7**—To walk along 55th Street, watching the growth of the new buildings and the rejuvenation of the University community. So wrote many letters and with great reluctance refused Albert's invitation to view the harness races, which is a fine technic for saving money. Reading now "Messalina," which fits beautifully into the series about "I, Claudius," by Robert Graves, and even Suetonius' "Lives of the Caesars."

**Aug. 8**—All the day at the desk, the weather having turned cold, and at night to dine sumptuously with Antoinette and Francois Pope, who demonstrated new lobster, crabmeat and shrimp dishes and some desserts so beautiful that one hesitated to disturb their prettiness with a fork. Here also were the Kerns and Philip Thorek and all the leaders of Swift's and Morrison Wood, and it made a fine evening.

**Aug. 9**—All the day, albeit Sunday, at the desk and viewing the hapless Cubs lose again in the ninth inning. In the evening to the home of Alfred Stepan in Winnetka for a garden party for the board and the workers of the Lyric Opera. Here Hemphill spoke and also Carol Fox. Chatted with Arnold Maremont of his recent trip to Russia, where tourism is a growing business. Met also young Stepan, who is studying at Oxford, and we chatted of the charm of that wonderful old university.

*(Continued on page A-249)*

**Aug. 10**—Early came Miss Wade and Miss Pierce of the Occupational Therapy Association to confer on their annual session. At noon to luncheon with Silvia Leiferman, who is full of ideas for our "Salute to Medical Research," and the trip to the club was repaid by seeing Henrietta Frieder, Rose Smith, Harriet Wolfson and a dozen other delightful damsels.

**Aug. 11**—At the desk until Justin came with the family, so all out to Ravisloe for golf and swimming.

**Aug. 12**—To lunch with Harry Scheer, talking of plastic models of the skeleton and the organs. In the afternoon with Dachman, Shamberg and the striking Miss Levy for further planning of the "Salute to Medical Research."

**Aug. 13**—To the club for golf and gin with the Goldblatts and saw the psychosomatic rejuvenation of the Cubs, who got 20 runs against the Giants. Finished the best-selling novel, "Celia Garth," which is about Charleston in revolutionary times, and it would put anyone to sleep.

**Aug. 14**—In the afternoon to the Union Station to meet Domna Dontas with Mistress Pepys and tried to pick them up but they were busy in conversation, and old Pepys ended in an altercation with the gendarmery. After a discussion of feminine vagaries, the gendarme was so overcome that he carried Mme. Dontas' suitcase a half block to the car.

**Aug. 15**—With Mme. Dontas to the Museum of Science and Industry. Next to view the University of Chicago and then to see the marriage of Theodora Bobrinskoy and Geoffrey Shepherd, who depart on a Fulbright scholarship to Glasgow. Here were Palmer, Ricketts and many others of the faculty. Then meeting Nick Dontas, and all to the reception at the Quadrangle Club. Next driving to Glencoe to the Pavilion, the most sumptuous dining place in the Chicago area next to the Pump Room, and to see the New York Ballet do "Serenade," "Fanfare" and a shocker called "The Cage."

**Aug. 16-18**—Three days of excessive heat, and most of the time at the desk.

**Aug. 19**—To the Tavern Club with Louis deBoer to discuss projects of the Chicago Heart Association. Stopped briefly to chat with Pete Akers of the *Sun-Times* and with Stephen Mitchell, who would like to be governor of Illinois. Then to see the new headquarters of the Chicago Heart Association in the process of construction in the State-Madison Building, and suggested a slogan: "The Chicago Heart Association over the world's busiest corner to help prevent the world's greatest medical problem." Next to meet with Ilza Veith and her committee at the Institute of Medicine to plan for a meeting dealing with medical history in Chicago in 1961.

**Aug. 20**—To Executive House, our newest hotel, and met with the committee that will sponsor the great banquet for medical research. Here were Oscar Getz, Mildred Romanoff, Francois Pope, Bill Margolis and all the staff members.

**Aug. 21**—The day being hot, with Justin and Ann and all their family to Ravisloe.

**Aug. 22**—Again blistering heat. Sat in the afternoon watching the White Sox go down to defeat, and read Alan Sillitoe's "Saturday Night and Sunday Morning," a novel of the proletariat who live in a little world all their own and yet basically have the same emotions that stir the nation's greatest tycoons. Reading also "Image of America," by R. L. Bruckberger, who explains the American democracy and how it differs from other democracies, and apparently this difference must be credited primarily to Thomas Jefferson. Father Bruckberger is a Dominican priest, and this and the fact that he served as chaplain in the Foreign Legion in the Sahara give his book a special flavor.

**Aug. 23**—This day came a half-dozen persons about to embark for Europe to consult Mis-

*(Continued on page A-250)*

THE PATIENT'S COMMENT

"I want to get a divorce on grounds of mental cruelty, like twice he tried to kill me."

"I left her because of another woman. Her mother."

"I'm sure I'm saner than the people who are attempting to cure me."

From "My Mind Went All to Pieces," by Robert Mines.

* * *

A CARL SANDBURG FAVORITE

Pat and Mike were at a wake. They became thirsty and decided to prop the corpse up between them and go across the street to a saloon. There they left the corpse for a few moments at the bar in the care of an innocent but somewhat obfuscated customer. He made several attempts to get friendly with the corpse until finally enraged he knocked the body over. Pat and Mike rushed over to sob dramatically, "You've killed him, you've killed him!"

Then came the retort, "I had to. He pulled a knife on me."

Told by Helga Sandberg in the *Saturday Review.*

* * *

tress Pepys on the best places to go and what to see and what to buy. For luncheon came Theodore Remer, who is also about to leave on his first trip abroad.

**Aug. 24**—At the desk and then early to New York, reading en route "Eva," by Meyer Levin, which tells again the story of a refugee girl and the miseries of the prison camps, with a contrived happy ending. In New York to find some cool weather once again. So to the Mayes' for dinner, and then to see a preview of Nevil Shute's "On the Beach." An all-star cast made the film impressive, but it was so morbid that its audience filed out without applause at the end.

**Aug. 25**—For a conference with Messrs. Runyon, Beebe, Stuttman and Whittemore on a new book. In the afternoon came Peter Warren, soon departing for Amsterdam, to discuss many more new projects now under way. In the evening to the Plaza, meeting Charles Haney and all his staff, who entertained at cocktails for visitors to the annual conference of the American Hospital Association. Here met Charles Wilinsky and Lilly, who were in good form, and with them Leo Lyons and his lady and Martha Iver from Corning, and many more administrators from far and near. Thereafter with Milton and Laura Runyon to New York's newest caravansary known as the Four Seasons. This is a beautiful, somewhat modernistic restaurant, one-half containing a great fountain and the other a great bar, with many unusual foods and particularly hors d'oeuvres such as are seldom seen, but one must be willing on entering to withdraw the entire savings account and entrust it to the major-domo.

Following is the report of a work-study engineer after a visit to a symphony concert at the Royal Festival Hall in London:

For considerable periods the four oboe players had nothing to do. The number should be reduced and the work spread more evenly over the whole of the concert period. This eliminates peaks of activity.

All 12 violins were playing identical notes. This is an unnecessary duplication. The staff of this section should be drastically cut. If larger volume of sound is required, it could be obtained by electronic apparatus.

Much effort was absorbed in the playing of demisemiquavers. It is recommended that all notes should be rounded up to the nearest semiquaver. If this were done it would be possible to use trainees and lower-grade operatives.

There seems to be too much repetition of some musical passages. Scores should be drastically pruned. No useful purpose is served by repeating on the horns a passage that has already been handled by the strings.

It is estimated that if all redundant passages were eliminated the whole concert time of two hours could be reduced to 20 minutes. The intermission should be eliminated.

The conductor agrees generally with these recommendations but expressed the opinion that there might be some falling off in box-office receipts. In that event, it should be possible to close sections of the auditorium entirely, with a consequential saving of overhead expenses, lighting, attendants, etc.

* * *

**Aug. 26**—Quite early came Bill Marsden and Ellwood Douglass, and we worked some hours on *World-Wide Abstracts*, ending with a luncheon in the men's bar at the Waldorf. Next came Max Geffen, Bill Lasdon, Bill White and Paul Robinson to consider a new venture in medical publishing. In the late afternoon to drive with Max Geffen out to Scarsdale and with Milton and Sylvia Lasdon off to the Old Oaks Country Club. Here was a duplicate bridge tournament in which Milton Lasdon and old Pepys finished fourth, but we would have finished second had not my enthusiastic partner redoubled, which is seldom warranted in a duplicate tournament.

**Aug. 27**—Quite early to the American Hospital Association Conference, meeting Martha Miller and spending a considerable time viewing the exhibits and seeing the marvelous management with which this meeting is conducted. Next in long telephone conferences with Tom Rivers on our congresses abroad, including one on congenital malformations and another on poliomyelitis. At noon came Miss Dorothy Chamberlain of *McCall's* to consider our contributions, and after that came young Steven Frey, who is soon to finish in foreign affairs at the University of Cincinnati. After an hour with Freeman Daniels on problems of legal import, to LaGuardia to fly on the jet to Chicago.

**Aug. 28**—The heat in Chicago blistering so spent all this day at the desk engaged in reading particularly Robert Penn Warren's new book "The Cave," which is a masterly piece of fiction.

**Aug. 29**—Early to the city to meet Drs. Frontali of Rome and Bossa of Naples and, after luncheon at the Standard Club, showed them some of Chicago, including the No. 1 Tour for physicians—a drive to the North Shore around the Edgewater Beach Hotel, back to the medical center around Cook County Hospital, then south to the University of Chicago and the Museum of Science and Industry. The tour was completed by a visit to our domicile for cool and refreshing drinks.

*(Continued on page A-252)*

# hen the distraction is intestinal . . .

tion study of the man in the second row rightly sadly speaks of diarrhea. And yet intestinal repose ld be his lot with POLYMAGMA. For POLYMAGMA tains Claysorb, which is more than five times as rptive as kaolin. It enlists two antibiotics work- synergistically. It permits a low-dose regimen with high effectiveness. And it has a taste and texture that wear well all through treatment.

* * *

In noninfectious diarrhea, you would, of course, prescribe POLYMAGMA Plain, having the same advanced formula but without antibiotics.

# olymagma®

rostreptomycin Sulfate, Polymyxin B Sulfate, and Pectin with Claysorb* (Activated Attapulgite, Wyeth) in Alumina Gel *Trademark

Wyeth

Philadelphia 1, Pa.

In the evening watched my first football of the season—the Detroit Lions against the New York Giants.

**Aug. 30**—To register at the Second World Conference on Medical Education, meeting Dag Knudsen, Stockholm, and from Chicago Turner, Hull, Bornemeier and Scatliff. Then chatting with Gilder of Canada and Bishop who is assistant to Louis Bauer. Next came Victor Johnson of Rochester testing out the short-wave translating mechanism. So took to lunch Ali of Karachi, Rasmussen of Denmark, Tornel of Barcelona, Dr. and Mrs. -A. Sison of Manila, Bossa of Naples and Frontali of Rome, and this is the delight of these international sessions.

**Aug. 31**—In the Grand Ballroom of the Palmer House some 1200 physicians assembled for the opening session of the Second World Conference on Medical Education sponsored by the World Medical Association. Some seven welcoming addresses fatigued the visitors, since there is nothing more to be said in welcoming anyone other than that he is welcome. Some inspiring speaker may some day discover a different way to say this. Dr. Raymond Allen spoke on "Medicine: A lifelong study," but most of the addresses were printed in the *Journal of the American Medical Association* which appeared on the Saturday preceding the congress, making it easy to avoid the congress if one wished to. Dr. Louis Bauer explained that the British had done this last time and the Americans presumably had to do it this time.

In the afternoon again at my work and in the evening to the great cocktail reception tendered by Mead Johnson where W. D. Snively, Jr. presided. Here met friends from far and wide including Otto Leuch of Zurich, Spinelli of Rome, Garcia Roselle of Peru, S. Wand of England, and many more. Thereafter to visit Andy's Epicurean Cafe on Wabash Avenue and found many of the visitors similarly enjoying what is about the most tasty cooking to be found anywhere.

### TAKING THE HISTORY

She was in a semiprivate room and could hear the intern taking the case history and examining a newly arrived patient.

"Have you had any operations?" the intern asked.

"Yes, I've had five. The first was for appendicitis."

Then followed a complete questioning regarding this first surgery—when, what age, what hospital, complications, etc.

"Okay," the intern finally said. "Now, these other four operations—were they for any particular reason?"

* * *

# The Medical Muse

RICHARD ARMOUR

### URINALYSIS

*Some bring their sample in a jar,*
*Some bring it in a pot,*
*Some bring a sample hardly ample,*
*While others bring a lot.*

*Some hide it in a paper bag,*
*Some wrap it like a treasure,*
*Some, quite undaunted, proudly flaunt it*
*As if it gives them pleasure.*

*Some cork it up so tightly that*
*It's quite a job to spring it,*
*Some let it slosh, almost awash,*
*And some forget to bring it.*

### FAR FROM THE MADDING PHONE

*A doctor's day off is a day for golf,*
*For hunting, for fishing, for hiking,*
*For dabbling with art, at least making a start*
*At painting, if that's what he's liking.*

*It's a day to relax with a hoe or an ax,*
*A day for a drive to the ocean,*
*It's twenty-four hours for sniffing the flowers*
*Or indulging the craziest notion.*

*Whatever he chooses, whatever amuses,*
*Whatever he does on his day off,*
*The doctor who's wise ought to realize*
*It had better be done somewhere 'way off!*